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Green and Scalable Palladium on Carbon-Catalyzed Tsuji-Trost Coupling Reaction Using an Efficient and Continuous Flow System

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Keywords: Tsuji-Trost coupling / Continuous flow / Allylic compound / Green chemistry

Abstract: The first continuous flow Tsuji-Trost coupling reaction between allylic compounds and various nucleophiles was successfully achieved within only ca. 40 s during the single-pass through a cartridge filled with palladium on carbon (Pd/C). Two methods have been designed using the H-cube ThalesNano technology and enable the efficient production of add-valued compounds in the gram-scale with high productivity. Under optimized conditions, the cartridge catalyst can be used for 60 minutes of continuous processing without a decrease in reactivity. A large diversity of substrates and nucleophiles were successfully submitted to the standard methods, with good to excellent yields and productivity.

Introduction

In the frame of green chemistry principles, the ability to conduct complex and routine transformations in a clean, sustainable and scalable way is highly desirable. In the past few years, the use of flow reactors with immobilized reagents in synthetic organic chemistry has been widely explored.[1] Systems use a device for delivering a substrate solution flowing through a cartridge filled with an heterogeneous catalyst. Among many advantages, this technology allows very efficient heat transfer compared with classical methodologies, good monitoring of temperature and enhanced mass transfer. Since the flow channel in the cartridge is sufficiently narrow, the reaction efficiency is expected to be enhanced due to the intimate contact of the catalyst with the substrate and reagents in comparison to a batch-type reaction using vessels or flasks. The immobilized catalyst – commonly a transistion-metal one – which often indicates a risk of ignition under atmospheric conditions, is enclosed in a sealed cartridge, allowing to secure the reaction. Moreover, flow process allows to avoid the problems associated with highly exothermic reactions and dangerous or moisture- and air-sensitive substrates. As a consequence, the reactions could be carried out in a safe manner. This innovative approach also permits the integration of several steps into one single streamlined process, thus shortening the time from research to pilot-scale and production.[2]

Coupling flow process with heterogeneous catalysis produces a synergistic effect. In fact, when the catalyst is immobilized in a cartridge, its recovery and reuse is simplified.[3] In addition, typical packed-bed reactors provide a high ratio of catalyst *vs.* substrate during the course of the reaction, an advantage that significantly increases the rate of reaction and simplifies the purification of the final products. However, some problems, such as leaching of Pd species, swelling of polymer supports, deposition of

products/by-products and poor catalyst cartridge life cycles can complicate their use in continuous flow systems.[4]

Metal-catalyzed cross-coupling chemistry has been widely used and studied during the last decades and showed a great impact both on the academic and industrial fields.[5] Lots of examples can be given covering the pharmaceutical,[6] material and polymer areas.[7] Many examples of metal-promoted continuous flow processes have been reported,[8] such as Suzuki-Miyaura cross-coupling aryl halides and boronic derivatives,[9] Negishi cross-coupling,[10] Heck coupling[11] or Sonogashira reaction.[12] Among all palladium mediated cross coupling reactions, Pd-catalyzed allylic substitution reactions are widely employed for constructing C-C, C-N, C-S and C-O bonds with high chemo-, regio- and stereoselectivities.[13] Indeed the so-called Tsuji-Trost reaction is very useful to introduce functional groups on the allylic position with a high regioselectivity on the less hindered carbon atom. Recently, we focused on this particular reaction for the bis-allylic substitution of DiVinylGlycol[14] and we also reported allylic substitution in a photochromic micellar medium.[15] Surprisingly the development of the Tsuji-Trost reaction in continuous flow systems was not yet described. Herein we report the design, scope and limitations of an efficient continuous flow allylic substitution protocol.

Results and Discussion

The flow-system used consisted of a ThalesNano H-cube®, a commercial packed bed flow hydrogenator. In our particular case, it was used only to work at high pressures and temperatures without any production of H_2. The reactants were dissolved in the adequate solvent and injected using integrated HPLC-type pump, and flowed into a cartridge packed with a predefined catalyst. The operating temperature was accurately controlled by the system during the process (Figure 1).[16] This system was used for

convenience but any set-up consisting of a pump, the cartridge, a way to heat the cartridge and a back pressure regulator could be used as well.

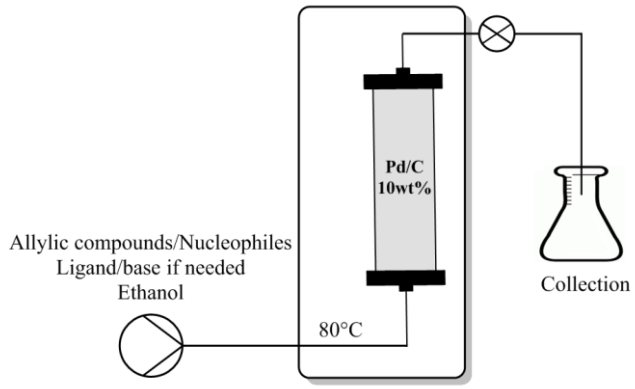
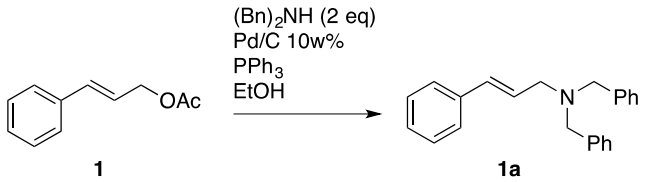


Figure 1. Experimental set-up of the flow system.

At first, we focused on the Tsuji-Trost reaction between cinnamyl acetate (**1**) and dibenzylamine (2 eq) in ethanol while using palladium on carbon (Pd/C) 10 w% as catalyst and triphenylphosphine. Among the supported catalytic systems available, Pd/C 10 w% is probably the most frequently used agent for industrial processes due to its low price, high catalytic activity and easy removal after completion of the reaction. It is also compatible with a wide range of solvents, including water.[17] As a consequence, the solution was passed through the catalyst cartridge (ca. 0.7 mL inside volume, loaded with 340 mg Pd/C 10w%) using the H-Cube ThalesNano apparatus. A first attempt was realized at 80°C with a flow rate of 1 mL min^{-1} leading to a conversion of 75% and 72% yield (Table 1, entry 1). Decreasing the flow rate to 0.5 mL min^{-1} allowed a significant improvement of the yield up to 90% (Table 1, entry 2). The same trend was observed when the reaction media was diluted to reach an excellent yield of 98% at 0.05 mol L^{-1} (Table 1, entries 3-5). Decreasing or increasing the temperature is deleterious for this reaction. In fact, at 60°C the conversion dropped to 21% (Table 1, entry 6) while working at 100°C promote the formation of by-products (Table 1,

entry 7). As expected, the conversion fell, to 21%, when the residence time is shortened (Table 1, entry 8). This result could be attributed to shorter contact time between substrates and catalyst. Besides, the use of triphenylphosphine is required for this reaction to achieved good results (Table 1, entry 9). According to the optimization results, two sets of conditions were compared. The first one, where the medium is diluted but affording excellent yield and conversion (Method A, Table 1, entry 5) and the second one leading to a better productivity (Method B, Table 1, entry 2).

Table 1. Optimization of the reaction conditions for the Pd/C catalyzed Tsuji-Trost coupling in flow.



1 **1a**

Entry	*T* (°C)	[**1**] (mol L^{-1})	PPh_3 (mol%)	Flow rate (mL min^{-1})	Residence time (s)	Conv.[a] (%)	Yield [a] (%)
1	80	0.5	10	1	42	75	72
2	80	0.5	10	0.5	84	91	90
3	80	0.2	10	1	42	92	91
4	80	0.1	10	1	42	94	94
5	80	0.05	10	1	42	98	98
6	60	0.05	10	1	42	21	16
7	100	0.05	10	1	42	96	81
8	80	0.05	10	2	21	21	15
9	80	0.05	0	1	42	15	4

[a] Determined by GC using dodecane as internal standard.

To explore further the scope of the allylic substitution reaction in continuous flow, different allylic acetates bearing aromatic or alkyl chain were submitted to the defined methods (methods A and B) with a variety of nucleophiles. At first, aromatic allylic acetates were selected as substrates. Excellent yields were achieved with cinnamyl acetate (**1**) using either nitrogen or sulfur nucleophiles (Table 2, entries 1-3). It is notable that the use of an additional base is required to deal with carbon and oxygen nucleophiles. Inorganic bases were first investigated such as K_2CO_3 or Na_2CO_3. As they are low soluble in ethanol, it appeared necessary to add water to solubilize them. In such conditions, a drop of the conversion and competitive saponification reaction of the substrate were observed. Furthermore, organic base were screened and tetramethylguanidine shown satisfactory results without any saponification (Table 2, entries 4-7). With Meldrum's acid, only the product **1d** resulting of the double alkenylation was isolated (Table 2, entry 4). Using the diketone derivative having only one hydrogen atom yielded to the desired product **1e** with 85% yield (Table 2, entry 5). While phenol could afford the corresponding ether **1f** in 71% yield under standard Method A (Table 2, entry 6), the more electro-enriched but much hindered 2-methoxy-4-methylphenol appears less reactive (Table 2, entry 7). As expected nitrophenol is totally inert in this process (Table 2, entry 8). The result for phenol is of particular interest as phenol, a weak nucleophile, is known for its low reactivity. In our standard conditions, to our satisfaction, this substrate reacted smoothly.

As expected, the branched aromatic allylic acetate derivative **2** was found to be less reactive, due to higher steric hindrance. Even with reduced flow rate, the conversion did not exceed 5 % (Table 2, entry 9). However, the racemic branched regioisomer of cinnamyl acetate **3** rearranges to the linear allylic products with all nucleophiles tested and gave good yields up to 98% (entries 10-13), comparable to those of linear cinnamyl acetate **1** (Table 2,

entries 1, 3, 5 and 7). This proved that, under standard Method A, the formation of the pi-allyl intermediate is not compromised.

In a second time, some aliphatic allylic acetates were submitted to the optimized conditions. The reaction between allyl acetate **4** and dibenzylamine was achieved with a moderate yield (Table 2, entry 14). The modification of the nucleophile *vs* allyl acetate **4** ratio (2/1 instead of 1/2) permit an improvement of the result to 67% yield. The length of the alkyl chain plays an important role in this process. In fact, the hexenyl acetate **5** afforded the amine **5a** in 41% yield while the nonadienyl acetate **6** reach an excellent yield of 91% (Table 2, entries 18 and 19). Interestingly, the reaction between the nonadienyl acetate **6** and phenol or tolylsulfinate salt afforded two compounds corresponding to the linear and the branched products with a ratio of 1/1 (Table 2, entries 20 and 21). In those particular cases, the regioselectivity of the reaction is not total and, surprisingly, more sterically hindered branched compounds are obtained. This could be due to interactions between the electron-rich double bound of the substrate and the aromatic ring of the nucleophile.[18] As expected, the diketone derivative reacted smoothly to give selectively the linear product **6f** in 82% yield (Table 2, entry 22). The disubstituted allyl acetate **7** derived from geraniol seems to be unreactive with this procedure. Only trace of the target compound **7a** has been detected (< 5%). This could be due to the presence of the branched methyl group on the double bound, hindering the formation or reactivity of the palladium intermediate.

Finally, with continuous interest for our research group, some biobased diallyl acetate substrate **8** was evaluated. In our hands, the allyl acetate **8** affords only the corresponding product **8a** in medium yield (Table 2, entries 24). Reducing the flow rate (0.3 mL min^{-1} *vs* 1 mL min^{-1}) gave no variation in the productivity of compound **8a**. This selectivity for the di-allylated product was previously noticed.[14]

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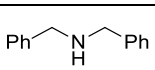
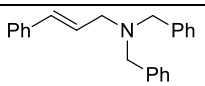
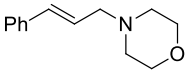
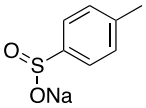
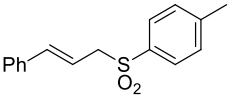
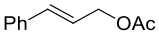
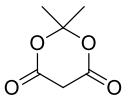
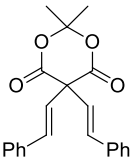
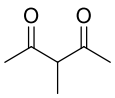
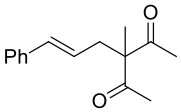
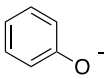
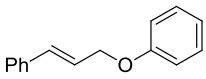
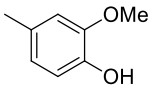
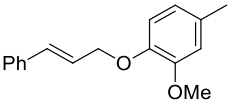
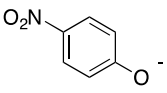
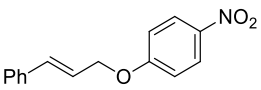
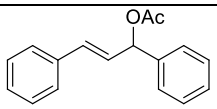
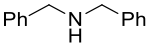
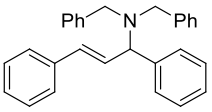
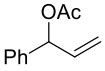
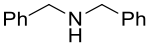
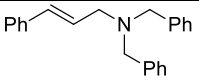
Table 2. Scope of the reaction with optimized methods A and B.[a]

Entry	Substrates	Nucleophiles	Products		Yield[e] (%) Method A	Yield[e] (%) Method B
1				**1a**	94	83
2				**1b**	97	93
3				**1c**	82	ND
4[b]				**1d**	63	47
5[b]	**1**			**1e**	85	71
6[b]				**1f**	71	ND
7[b]				**1g**	58	48
8[b]				**1h**	0	ND
9	 **2**			**2a**	<5	ND
10				**1a**	92	ND

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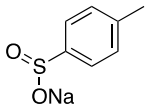
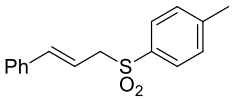
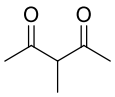
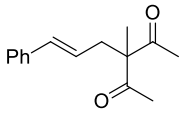
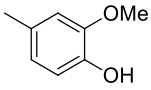
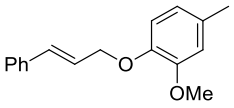
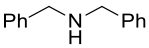
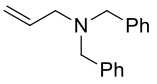
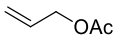
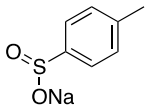
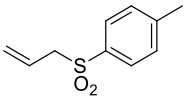
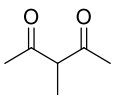
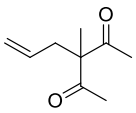
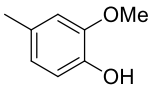
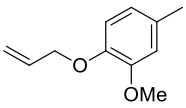
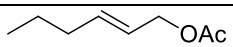
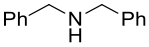
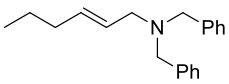
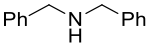
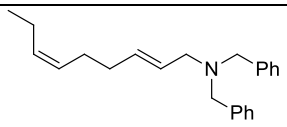
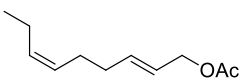
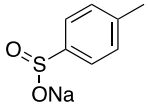
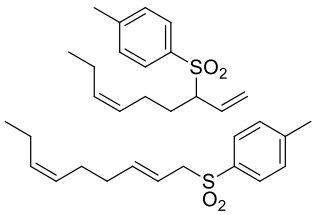
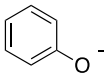
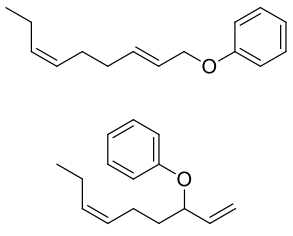
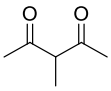
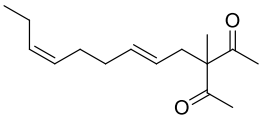
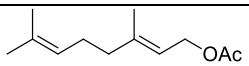
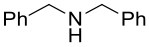
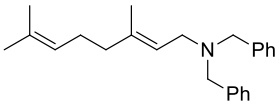
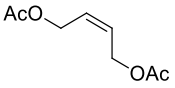
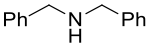
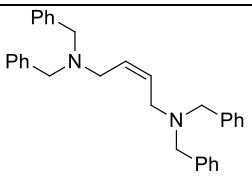
11	**3** +/-			**1c**	81	ND
12[b]				**1e**	98	ND
13[b]				**1g**	65	ND
14				**4a**	52 67[c]	ND 95[c]
15				**4b**	71[c]	ND
16[b]	**4**			**4c**	44[c]	48[c]
17[b]				**4d**	50[c]	76[c]
18	 **5**			**5a**	41	ND
19				**6a**	91	ND
20	 **6**			**6b** **6c**	80 L:B 1:1	ND
21[b]				**6d** **6e**	61 L:B 1.3:1	ND

22[b]				**6f**	82	ND
23	 **7**			**7a**	<5	ND
24	 **8**		 (Z/E 85 :15)	**8a**	53 54[d]	ND

[a] Method A: Substrate (1 mmol), Nucleophile (2 mmol), PPh_3 (0.1 mmol), EtOH (20 mL), flow rate 1 mL min^{-1}. Method B: Substrate (5 mmol), Nucleophile (10 mmol), PPh_3 (0.5 mmol), EtOH (10 mL), flow rate 0.5 mL min^{-1}. [b] Addition of tetramethylguanidine (2 mmol for Method A or 10 mmol for Method B) as base. [c] Ratio Substrate/Nucleophile 2/1. [d] Flow rate 0.3 mL min^{-1}. [e] Isolated yield.

To gain in productivity a second set of conditions was evaluated, referred as Method B (Table 1, entry 2). The concentration is tenfold higher than in Method A. In consequence, the flow rate should be decreased to reach high yield. The cinnamyl acetate (**1**) gave good yield lower to those obtained with the method A (Table 3, entries 1-6). With a nucleophile *vs* substrate ratio of 2/1, the allylic substitution of allyl acetate **4** with various nucleophiles was more efficient than in Method A (Table 3, entries 7-9).

Finally, the stability of the supported catalyst was investigated. At first, the same cartridge was reemployed for the Tsuji-trost reaction between cinnamyl acetate (**1**) and dibenzylamine. It was found that after 6 consecutive runs the yield dropped to 91% and decreased gradually to 70% after 17 runs. The calculated turnover number (TON) was higher than 40 for the method A and close to 30 for the method B. Then the behavior over the time of the catalyst

for both methods on the standard reaction has been studied. A long run was performed, 6h for method A and 3h for method B (Figure 2). For method A, the yield became to drop smoothly after 60 minutes of reaction. For method B the activity of the catalyst dropped dramatically after 30 minutes and then decreased gradually to 40% after 3h of reaction. Leaching of palladium was determined using ICP with a standard curve for the coupling reaction at less than 60 ppb after 1 hour of reaction for Method A. These results demonstrate the low level of leaching of metal catalyst from the support.

Conclusions

In present study, a clean, mild, reproductible and scalable continuous flow process for Tsuji-Trost cross-coupling reaction using a Pd/C 10 w% supported catalyst has been developed. A wide scope of different substrates has been successfully submitted to the optimized protocols, leading to the target products with good to excellent yields. Except for 2 examples, a total selectivity for the linear products has been observed. The stability of the catalyst over 60 minutes of continuous run is worth noting. The affordable price of the supported catalyst and the efficiency of the reaction make this procedure a practical alternative to perform allylic substitutions.

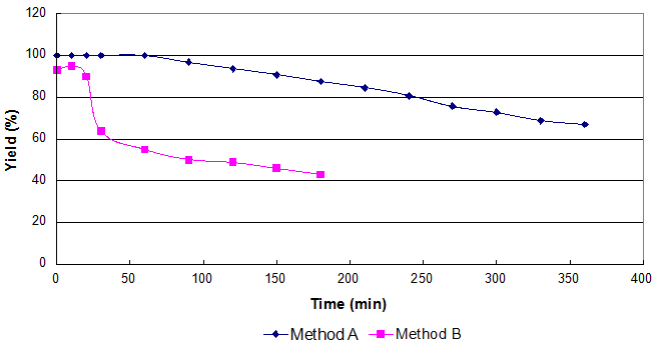


Figure 2. Tsuji-Trost reaction between cinnamyl acetate and dibenzylamine (Method A in blue, Method B in pink).

Experimental Section

General: All commercially available products and solvents were used without further purification. Reactions were monitored by TLC (Kieselgel 60F254 aluminum sheet) with detection by UV light or phosphomolybic acid solution. Column chromatography was performed on silica gel 40−60 μm. Flash column chromatography was performed on an automatic apparatus, using silica gel cartridges. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz/54 mm ultralong hold. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to TMS as an internal standard. Coupling constants (J) are quoted in hertz.

Synthesis

General flow procedure (Method A) for Preparation of 1a-g, **4a-d**, **5ab6a-f and 8a.** A solution containing the allylic acetate (1 mmol), the nucleophile (2 mmol), triphenylphosphine (0.1 mmol, 25mg) and tetramethylguanidine (2 mmol, 230 mg) when required, in technical ethanol (20 mL) were pumped at 1 mL min^{-1} using the H-cube ThalesNano system. The solution was passed through a cartridge filled with Pd/C 10w% (ca 340 mg) at 80°C, giving a residence time of 0.7 min. The outlet solution was evaporated to dryness and submitted to flash chromatography on silica (cyclohexane/EtOAc) to afford compounds **1a-g**, **4a-d**, **5ab6a-f**, **8a** and **9a**.

General flow procedure (Method B) for Preparation of 1a, 1b, 1d-g, **4a, 4c and 4d.** Method B. A solution containing the allylic acetate (5 mmol), the nucleophile (10 mmol), triphenylphosphine (0.5 mmol, 125mg) and tetramethylguanidine (10 mmol, 1,15 g) when required, in technical ethanol (10 mL) were pumped at 0.5 mL min^{-1} using the H-cube ThalesNano system. The solution was passed through a cartridge

filled with Pd/C 10w% (ca 340 mg) at 80°C, giving a residence time of 0.7 min. The outlet solution was evaporated to dryness and submitted to flash chromatography on silica (cyclohexane/EtOAc) to afford compounds **1a, 1b, 1d-g**, **4a, 4c** and **4d**.

(E)-*N,N*-Dibenzyl-3-phenylprop-2-en-1-amine (**1a**).[19] Prepared according to Method A as pale yellow oil; yield 295 mg (94%). Prepared according to Method B as pale yellow oil; yield 1.378 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 – 7.14 (m, 15 H), 6.58 (d, J = 15.9 Hz, 1 H), 6.35 (dt, J = 15.9, 6.5 Hz, 1 H), 3.68 (s, 3 H), 3.27 (d, J = 6.3 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.65, 137.22, 132.49, 128.82, 128.54, 128.25, 127.80, 127.33, 126.87, 126.28, 57.96, 55.79 ppm.

4-Cinnamylmorpholine (**1b**).[5d] Prepared according to Method A as pale yellow oil; yield 197 mg (97%). Prepared according to Method B as pale yellow oil; yield 950 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.19 (m, 5 H), 6.56 (d, J = 15.9 Hz, 1 H), 6.28 (dt, J = 15.8, 6.9 Hz, 1 H), 3.76 (dd, J = 10.9, 6.2 Hz, 4 H), 3.20 (dd, J = 6.9, 1.3 Hz, 2 H), 2.60 (d, J = 32.7 Hz, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.68, 133.86, 128.60, 127.68, 126.37, 125.36, 66.73, 61.28, 53.42 ppm.

***trans*-Cinnamyl-*p*-tolyl Sulfone** (**1c**).[5d] Prepared according to Method A as white solid; yield 224 mg (82%); m.p. 120°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.2 Hz, 2 H), 7.38 – 7.25 (m, 7 H), 6.41 (d, J = 15.8 Hz, 1 H), 6.23 – 6.03 (m, 1 H), 3.95 (d, J = 7.5 Hz, 2 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.76, 139.02, 135.83, 135.52, 129.73, 128.67, 128.53, 128.49, 126.63, 115.35, 60.57, 21.66 ppm.

5,5-Dicinnamyl-2,2-dimethyl-1,3-dioxane-4,6-dione (1d).[5d] Prepared according to Method A as white solid; yield 412 mg (63%). Prepared according to Method B as white solid; yield 409 mg (47%). m.p. 130°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 – 7.16 (m, 10 H), 6.57 (d, J = 15.8 Hz, 2 H), 6.11 (dt, J = 15.7, 7.8 Hz, 2 H), 2.98 (d, J = 7.8 Hz, 2 H), 1.58 (d, J = 12.9 Hz, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.78, 136.21, 135.99, 128.66, 127.99, 126.35, 121.72, 106.07, 56.35, 42.12, 29.79 ppm.

3-Cinnamyl-3-methylpentane-2,4-dione (1e).[20] Prepared according to Method A as a colorless oil; yield 196 mg (85%). Prepared according to Method B as a colorless oil; yield 817 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 – 7.20 (m, 5 H), 6.48 (dd, J = 14.9, 13.7 Hz, 1 H), 6.08 – 5.91 (m, 1H), 2.76 (dd, J = 7.5, 1.3 Hz, 2 H), 2.16 (s, 6 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.78, 136.87, 134.04, 128.54, 127.51, 126.21, 123.96, 66.75, 38.05, 26.76, 18.29 ppm.

(Cinnamyloxy)benzene (1f).[21] Prepared according to Method A as white solid; yield 150 mg (71%). Prepared according to Method B as white solid; yield 751 mg (71%). m.p. 70°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, J = 7.5 Hz, 2 H), 7.26 – 7.10 (m, 5 H), 6.86 (dd, J = 7.5, 5.0 Hz, 3 H), 6.62 (d, J = 16.0 Hz, 1 H), 6.31 (dt, J = 16.0, 5.8 Hz, 1 H), 4.64 – 4.50 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.71, 136.54, 133.02, 129.59, 128.68, 127.97, 126.67, 124.60, 120.98, 114.85, 68.60 ppm.

1-(Cinnamyloxy)-2-methoxy-4-methylbenzene (1g). Prepared according to Method A as white solid; yield 148 mg (58%). Prepared according to Method B as white solid; yield 610 mg (48%). m.p. 70°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (d, J = 7.7 Hz, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.31 – 7.23 (m, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.79 – 6.70 (m, 3 H), 6.49 (dt, J

= 16.0, 5.9 Hz, 1 H), 4.77 (dd, *J* = 5.9, 1.1 Hz, 2 H), 3.91 (s, 3 H), 2.34 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.30, 145.83, 136.56, 133.07, 131.02, 128.56, 127.82, 126.62, 124.90, 120.82, 113.80, 112.79, 69.96, 55.85, 21.08 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{19}O_2$ 255.1385, Found 255.1421.

***N,N*-dibenzylprop-2-en-1-amine (4a).**[22] Prepared according to Method A, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 158 mg (67%). Prepared according to Method B, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 1.17 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 10 H), 5.96 (dd, *J* = 15.1, 8.3 Hz, 1 H), 5.34 – 5.14 (m, 1 H), 3.62 (s, 4 H), 3.10 (brs, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.70, 136.02, 128.79, 128.21, 126.83, 117.36, 57.75, 56.35 ppm.

1-(Allylsulfonyl)-4-methylbenzene (4b).[23] Prepared according to Method A, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 140 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 – 7.73 (m, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 5.80 (ddt, *J* = 17.4, 10.1, 7.4 Hz, 1 H), 5.34 (dd, *J* = 10.1, 0.7 Hz, 1 H), 5.16 (dq, *J* = 17.1, 1.1 Hz, 1 H), 3.80 (d, *J* = 7.4 Hz, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.75, 135.36, 129.69, 128.51, 124.81, 124.59, 60.96, 21.65 ppm.

3-Allyl-3-methylpentane-2,4-dione (4c).[24] Prepared according to Method A, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 68 mg (44%). Prepared according to Method B, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 369 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 – 5.48 (m, 1 H), 5.16 – 5.03 (m, 2 H), 2.59 (d, *J* = 7.3 Hz, 2 H), 2.14 – 2.09 (m, 6 H), 1.33 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.73, 132.46, 119.08, 66.42, 38.77, 26.67, 18.06 ppm.

1-(Allyloxy)-2-methoxy-4-methylbenzene (4d). Prepared according to Method A, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 90 mg (50%). Prepared according to Method B, using allylic acetate (2 mmol) and nucleophile (1 mmol), as a yellow oil; yield 682 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (dd, J = 11.3, 7.2 Hz, 1 H), 6.76 – 6.66 (m, 2 H), 6.10 (ddt, J = 17.2, 10.7, 5.4 Hz, 1 H), 5.41 (ddd, J = 17.3, 3.0, 1.4 Hz, 1 H), 5.29 (ddd, J = 10.5, 2.7, 1.3 Hz, 1 H), 4.60 (dt, J = 5.4, 1.4 Hz, 2 H), 3.88 (s, 3 H), 2.32 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.25, 145.77, 133.64, 130.91, 120.73, 117.78, 113.68, 112.81, 70.09, 55.83, 21.04 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for C11H15O2 179.1072, Found 179.0856.

(E)-*N*,*N*-dibenzylhex-2-en-1-amine (5a).[25] Prepared according to Method A as a yellow oil; yield 116 mg (41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.17 (m, 10 H), 5.71 – 5.44 (m, 2 H), 3.59 (s, 4 H), 3.03 (d, J = 5.7 Hz, 2 H), 2.04 (dd, J = 13.5, 6.8 Hz, 2 H), 1.46 – 1.36 (m, 2 H), 0.92 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.90, 134.01, 128.82, 128.15, 127.26, 126.73, 57.61, 55.53, 34.57, 22.54, 13.71 ppm.

(2E,6Z)-*N*,*N*-Dibenzylnona-2,6-dien-1-amine (6a).[25] Prepared according to Method A as a yellow oil; yield 290 mg (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.19 (m, 10 H), 5.69 – 5.51 (m, 2 H), 5.48 – 5.29 (m, 2 H), 3.58 (s, 4 H), 3.03 (d, J = 5.5 Hz, 2 H), 2.18 – 1.98 (m, 6 H), 0.96 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.88, 133.45, 132.04, 128.81, 128.40, 128.15, 127.58, 126.73, 57.66, 55.54, 32.60, 27.00, 20.58, 14.34 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{30}N$ 320.2378, Found 320.1842.

1-Methyl-4-((2E,6Z)-nona-2,6-dien-1-ylsulfonyl)benzene (6b) and (Z)-1-methyl-4-(nona-1,6-dien-3-ylsulfonyl)benzene (6c). Prepared according to Method A as a yellow oil; yield 111 mg (40%) of compound **6b** and 112 mg (40%) of compound **6c**. For compound **6b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.9 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 5.60 – 5.15 (m, 4 H), 3.74 (d, J = 7.1 Hz, 2 H), 2.46 (s, 3 H), 2.13 – 1.93 (m, 6 H), 0.95 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.52, 134.45, 133.57, 130.31, 129.43, 129.24, 126.61, 123.72, 69.23, 26.98, 23.88, 21.64, 20.62, 14.22 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}O_2S$ 279.1419, Found 279.1478. For compound **6c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.1 Hz, 2 H), 7.34 (d, J = 8.1 Hz, 2 H), 5.63 (dt, J = 17.2, 9.7 Hz, 1 H), 5.49 – 5.37 (m, 1 H), 5.33 (d, J = 10.2 Hz, 1 H), 5.29 – 5.17 (m, 1 H), 5.07 (d, J = 17.1 Hz, 1 H), 3.58 – 3.44 (m, 1 H), 2.46 (s, 3 H), 2.18 – 1.90 (m, 5 H), 1.79 – 1.65 (m, 1 H), 0.99 – 0.89 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.52, 134.45, 133.57, 130.31, 129.43, 129.24, 126.61, 123.72, 69.23, 26.98, 23.88, 21.64, 20.62, 14.22 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}O_2S$ 279.1419, Found 279.1397.

1-((2E,6Z)-Nona-2,6-dienyloxy)benzene (6d) and 1-((Z)-nona-1,6-dien-3-yloxy) benzene (6e). Prepared according to Method A as a yellow oil; yield 132 mg (61%) of a mixture of **6d** and **6e** (1.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 4H, HAr), 6.99 – 6.92 (m, 6 H, HAr), 5.93 – 5.73 (m, 3H, CH=CH), 5.45 – 5.35 (m, 4H, CH=CH), 5.31 – 5.20 (m, 2H, CH=C$\underline{H}_{2\ \text{branched}}$), 4.63 ($q_{app}$, J = 5.7 Hz, CH-O $_{\text{branched}}$), 4.51 (d, J = 5.8 Hz, 2H, CH_2-O $_{\text{linear}}$), 2.25 – 1.58 (m, 12H, CH_2), 0.99 (t, J = 7.5 Hz, 3H, $CH_{3\ \text{linear}}$), 0.94 (t, J = 7.5 Hz, 3H, $CH_{3\ \text{branched}}$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.73, 158.43, 138.07, 134.95, 132.65, 132.31, 129.42, 129.29, 128.07, 127.98, 125.23, 120.70, 120.67, 116.44, 116.02, 114.75, 78.16, 68.67, 35.63, 32.48, 26.62, 22.99, 20.60, 20.54, 14.35, 14.28 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{21}O$ 217.1592, Found 217.1608.

3-Methyl-3-((2E,6Z)-nona-2,6-dien-1-yl)pentane-2,4-dione (6f). Prepared according to Method A as a yellow oil; yield 195 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57 – 5.47 (m, 1 H), 5.42 – 5.34 (m, 1 H), 5.32 – 5.15 (m, 2 H), 2.55 (dd, *J* = 7.1, 6.5 Hz, 2 H), 2.15 – 1.98 (m, 12 H), 1.31 (s, 3H), 0.96 (t, *J* = 7.5 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.03, 134.81, 132.14, 128.14, 123.91, 66.64, 37.62, 32.65, 26.89, 26.74, 20.55, 18.09, 14.31 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{25}O_2$ 237.1855, Found 237.1795.

(Z)- and (E)-*N*^{1},*N*^{1},*N*^{4},*N*^{4}-Tetrabenzylbut-2-ene-1,4-diamine (8a). Prepared according to Method A as a white solid; yield 244 mg (53%) of a mixture of (Z)-isomer and (E)-isomer in ration 85:15; m.p. 111°C. For the (Z) isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.23 (m, 20 H), 5.78 (s, 2 H), 3.63 (s, 8 H), 3.12 (s, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.71, 130.75, 128.81, 128.23, 126.86, 57.81, 55.25 ppm. For the (E) isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 – 7.23 (m, 20 H), 5.78 (s, 2 H), 3.57 (s, 8 H), 3.06 (d, *J* = 3.8 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 139.71, 130.20, 128.81, 128.23, 126.86, 58.09, 57.81 ppm. HRMS (EI) m/z: $[M+H]^+$ Calcd for $C_{32}H_{35}N_2$ 447.2800, Found 447.2351.

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