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An efficient chemoselective strategy for the preparation of (*E*)-cinnamic esters from cinnamaldehydes using heterogeneous catalyst and DDQ☆

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Abstract—An efficient chemoselective protocol is developed for the synthesis of (*E*)-cinnamic esters from substituted cinnamaldehydes or cinnamyl alcohols using a combination of DDQ and heterogeneous catalyst under microwave irradiation. The method showed remarkable selectivity for cinnamaldehydes over aliphatic and aromatic aldehydes, which is a novel finding. The results demonstrate that the developed protocol can be a useful synthetic tool for chemoselective esterification in total synthesis of complex organic compounds.

1. Introduction

(*E*)-Cinnamic esters are immensely important organic compounds due to their application in a wide range of industrial products such as plasticizers, graphics, lubricants, flavours, perfumes and cosmetics.[1] For example, 2-ethylhexyl-4-methoxycinnamate is a UV absorbing sunscreen agent and a common ingredient in most of the new sunscreen lotions and many other cosmetic formulations.[1] Further, these α,β-unsaturated esters possess various pharmacological activities including antioxidant, antimicrobial and anticancer activities,[2] besides being useful in other synthetic applications.[3] Numerous methods[4] have been reported for the preparation of α,β-unsaturated esters, however, most of the reported procedures require strong acids[5] like sulfuric acid, hydrochloric acid, and toxic chemicals[6] such as dimethylsulfate, methyl iodide and diazomethane, which are environmentally hazardous and hence unacceptable. More importantly, none of the methods disclose a single-step approach towards conversion of cinnamaldehydes into cinnamic esters, while simultaneously taking care of the compatibility of the process with other sensitive functional groups.[4–6] In this context, the protocol developed by Corey et al.[7] assumes special significance as it demonstrated a mild and direct conversion of cinnamaldehydes into cinnamic esters without affecting any other sensitive functional groups.

This revolutionary method made a remarkable impact in organic synthesis and has been instrumental in the synthesis of various complex natural products.[8] The above method continued to attract the attention of researchers for direct conversion of aldehydes or alcohols into esters and various reports have surfaced with some modifications in the original method using a range of reagents such as MnO_2–NaCN,[9] chromium oxide–pyridine,[10] TMSCN[11] and *tert*-butyl hypochlorite,[12] etc. For example, Foot et al.[9c,d] described a facile and direct oxidative esterification of cinnamyl alcohols to the corresponding cinnamic esters using a combination of MnO_2–NaCN in alcohol. Similarly, Bal et al.[11] accomplished the direct transformation of α,β-unsaturated aldehydes to the corresponding esters utilizing TMSCN.

Though meticulous, the above protocols for direct conversion of cinnamaldehydes or cinnamyl alcohols (C_6–C_3 unit) into cinnamic esters (C_6–C_3 unit) remain impregnated with some limitations. Apart from expensive reagents and delicate reaction conditions, some of these methods[7–9,11] also pass through an intermediate C_6–C_4 unit, formed by the combination of substrate (C_6–C_3 unit) and an extra C_1 unit in the form of toxic sodium/potassium cyanide[7–9] or TMSCN,[11] thereby conferring lack of atom economy[13] on these protocols. Further, the above methods[7–9] produce toxic hydrogen cyanide gas as a by-product, which severely limits their industrial applications. Consequently, there have been some reports disclosing the direct esterification of cinnamyl alcohols utilizing dimethyl acetate/trimethyl formate/*meta*-chloroperbenzoic acid[14] or hypervalent iodine (III) reagent[15] in lieu of toxic sodium/potassium cyanide.[7–9] Recently, some reports employing selective,[16] atom economical methodologies[17] or utilizing heterogeneous recyclable catalyst[18] for the synthesis of (*E*)-cinnamic esters have also surfaced. Though the above-mentioned methodologies are environmentally

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benign, the expensive nature of the reagent limits their widespread utility.

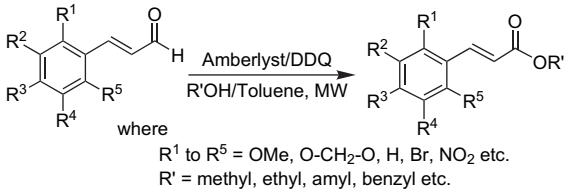
It is thus evident that there remains a wide scope for the development of clean and efficient[19] methodologies for direct transformation of cinnamaldehydes or cinnamyl alcohols into the corresponding esters. The recent years have witnessed a tremendous upsurge of interest in using recyclable reagents and heterogeneous catalysts[20] for various chemical transformations due to their inherent economic and environmental benefits.[21] Reactions assisted by heterogeneous catalysts have revolutionized the domain of organic synthesis due to higher yields, easy work up, recyclability of the catalysts and consequent minimization of waste production. Similarly, microwave[19] induced synthesis has become the flavour of contemporary organic research due to its spectacular benefits like enhancement in reaction rates and yields, and the attendant advantages of energy efficiency. In this context, we herein wish to report an efficient and chemoselective methodology for the preparation of various (*E*)-cinnamic esters from cinnamaldehydes or cinnamyl alcohols in one pot using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[21] and heterogeneous catalyst under microwave.

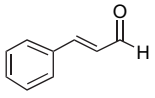
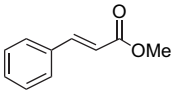
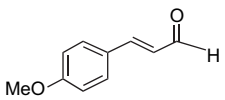
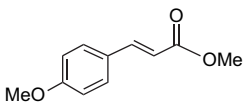
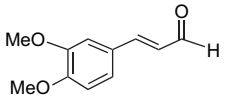
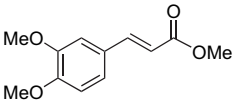
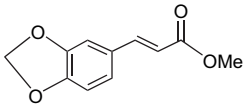
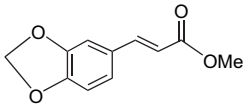
2. Results and discussion

In continuation of our unflinching strive for microwave-assisted synthesis of bioactive compounds,[22] it was fascinating to develop an effective methodology for conversion of cinnamaldehydes into cinnamates in one step with the help of DDQ as an oxidizing agent[21,23] and a heterogeneous catalyst. To begin with, cinnamaldehyde (**1a**) was treated with DDQ (1.2 equiv) and methanol in catalytic amount of Amberlyst-15 for 24 h or refluxed for 10 h, which provided methyl cinnamate (**1b**) in 81% and 83% yield, respectively (Scheme 1). To further increase the yield of the product, various alterations in the reaction conditions were made. Oxidants such as chloranil, manganese dioxide and pyridinium chlorochromate[24] were tried, but these greatly reduced yields of **1b** up to 10–15%. After a lot of experimentation, it was found that performing the above reaction with the addition of high boiling solvent toluene to a mixture of **1a**, DDQ (1.5 equiv), Amberlyst-15 and methanol under Dean–Stark not only reduced the reaction time from 10 to 6 h but also increased the yield of **1b** from 83% to 92%. Our desire to further reduce the reaction time prompted us to undertake the above reaction under microwave irradiation. To our delight, microwave not only curtailed the reaction time from 6 h to 30 min, but also increased the yield up to 96%. After success of **1b**, the method was extended to various other substrates like substituted cinnamaldehydes (entries 2a–10a), cinnamyl alcohols (entries 11a and 12a), aromatic and aliphatic aldehydes (entries 13a–16a, Table 1). It is clear from Table 1 that yield of all the methoxy substituted cinnamic esters (entries 2b–9b) is comparable among themselves as well as with unsubstituted ester (entry 1b).

Scheme 1.

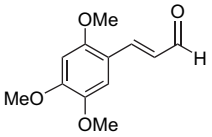
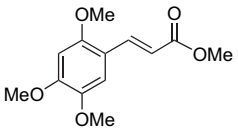
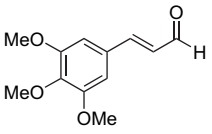
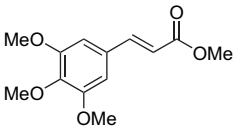
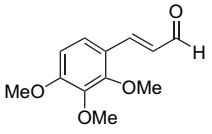
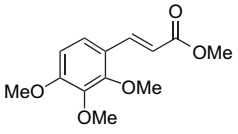
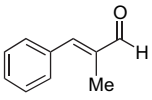
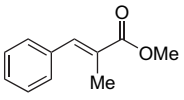
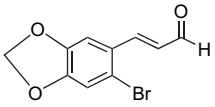
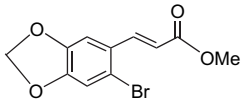
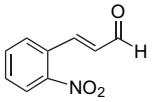
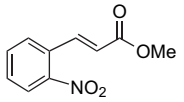
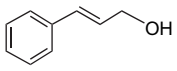
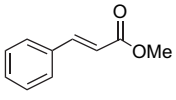
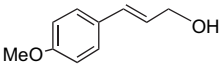
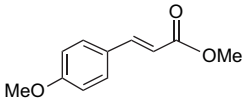
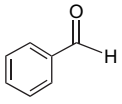
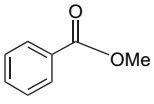
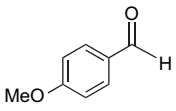
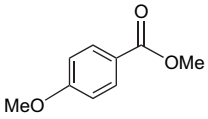
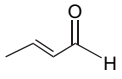
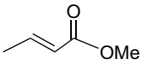
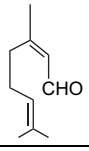
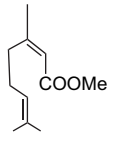
Table 1. Synthesis of (*E*)-cinnamic esters from cinnamaldehydes or cinnamyl alcohols[a]



Entry	Substrate (a)	Reaction time (min)	Product (b)	Yield[b] (%)	Reference
1		30		96	4i,25j
2		35		92	25b,c,j
3		35		91	4a,25c
4		40		89	25j

(*continued*)

Table 1. (*continued*)

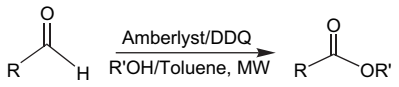
Entry	Substrate (a)	Reaction time (min)	Product (b)	Yield[b] (%)	Reference
5		35		92	25c,i
6		35		91	26
7		40		89	26
8		60		51	25e
9		50		63	26
10		120		7	25f
11		50		90[c]	4i,25j
12		50		87[c]	25b,c,j
13		120		0	9b
14		120		0	9b
15		120		0	26
16		120		0	26

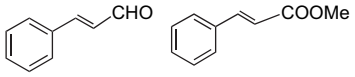
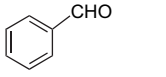
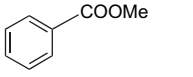
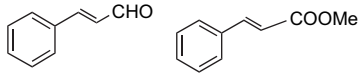
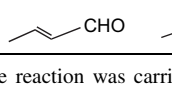
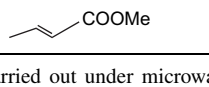
[a] The reaction was carried out under microwave fitted with Dean–Stark apparatus, using **1a** (37.5 mmol), DDQ (56.3 mmol), MeOH (4–5 mL), toluene (25 mL) and Amberlyst-15 (0.1–0.2 g).
[b] Yield of the isolated product based on **1a**.
[c] Amount of DDQ used, 75 mmol.

Further, the yield was low in the case of α-methyl and 2-bromo substituted cinnamic esters (entries 8b and 9b), while the ester (entry 10b) was formed only in traces (7% based upon NMR analysis of crude product) in the case of 2-nitrocinnamaldehyde even upon irradiation for 120 min. It is worthwhile to note that a couple of the above reactions were also performed in DDQ alone, i.e., without any Amberlyst-15, however, no product was formed even after 120 min of irradiation. This proves beyond doubt, the utility of heterogeneous catalyst.

It is also evident from Table 1 that benzaldehydes (entries 13a and 14a) as well as the aliphatic aldehydes (entries 15a and 16a) did not undergo the above reaction, thus indicating a probable chemoselectivity towards cinnamaldehydes as compared to aromatic or aliphatic aldehydes. In order to test this hypothesis, the above method was subjected to an equimolar mixture of cinnamaldehyde and aromatic aldehyde (Table 2). To our surprise, cinnamaldehyde got preferentially esterified in comparison to the aromatic aldehyde. Similarly, cinnamaldehyde was selectively esterified in comparison to the aliphatic aldehyde (Table 2). The evident indispensable requirement of an aromatic ring with α,β-unsaturated aldehydic side chain is an interesting facet, and to the best of our knowledge has been reported for the first time. It is pertinent to mention here that this pronounced selectivity can be a significant addition to the growing arsenal for chemoselective esterification in total synthesis of complex organic compounds including natural products.

Table 2. Esterification of equimolar mixtures of cinnamaldehyde and benzaldehyde (entry 1), cinnamaldehyde and crotonaldehyde (entry 2)[a]



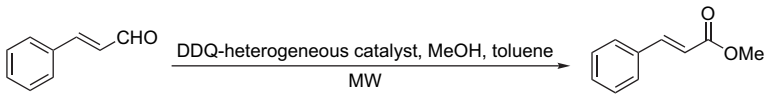
Entry	Substrate	Product	Reaction time (min)	Yield (%)	Conversion (%)
1			50	92	100
				0	0
2			50	90	100
				0	0

[a] The reaction was carried out under microwave fitted with Dean–Stark apparatus using both the substrates in 1:1 ratio (18.75 mmol each), DDQ (56.3 mmol), MeOH (4–5 mL), toluene (20–25 mL) and Amberlyst (0.2 g).

In order to ascertain the efficacy of the heterogeneous catalyst, a variety of them were scanned for esterification of **1a** with methanol into **1b** and the results are shown in Table 3. The order of the activities of various catalysts was found to be Amberlyst-15>neutral alumina>Amberlyte IR-120> acidic alumina>silica gel (60–120 mesh). It may be mentioned here that organic acids like acetic acid and *p*-toluenesulfonic acid were also tried and found effective (88% yield). However, the approach suffers from several limitations vis-à-vis the use of heterogeneous catalyst, as not only does it entail subsequent neutralization and tedious workup, but also the use of non-recyclable chemicals, which goes against the basic tenets of ecofriendly chemical practices.[13]

Similarly, the impact of nature of alcohol (Table 4) on the esterification reaction with cinnamaldehyde (**1a**) was also examined and it was found that MeOH provided maximum yield of the corresponding methyl esters in comparison to other alcohols. Also that branching in the structure of the alcohol seems to reduce the yield of the ester as in the case of isopropyl and isoamyl alcohols (entries 6 and 7) while tertiary butanol (entry 8) did not give any product. Further, the diol (entry 9) provided poor yield of the ester while its mono methylated counterpart (entry 10) gave excellent yield. Interestingly, cinnamyl alcohol (entry 11) gave only 5% of the expected esterification product, with the bulk of the alcohol being oxidized by DDQ to cinnamaldehyde as is evident from Table 4. Further, no formation of the ester was observed in the case of 1-phenyl-1-propanol (entry 12) or benzyl alcohol (entry 13), rather the alcohols were oxidized to 1-phenyl-1-propanone and benzaldehyde, respectively, under these conditions and **1a** was recovered unreacted. However, 3-phenyl-1-propanol (entry 14) did give 3-phenylpropyl-3-phenylpropenoate, an important cytotoxic ester,[2a] in 89% yield. These observations apparently reflect the relative tendency of DDQ to oxidize benzylic alcohols. It may be mentioned here that the applicability of this method to wide range of alcohols (Table 4) is a significant improvement over the earlier methods, which were mostly limited to methanol, ethanol or *n*-butanol.[7–9,17,18]

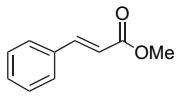
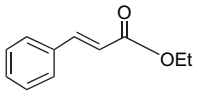
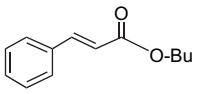
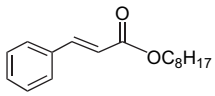
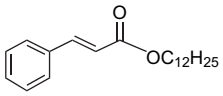
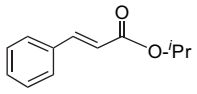
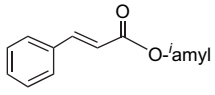
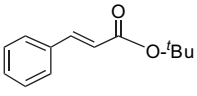
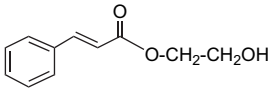
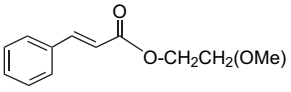
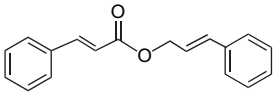
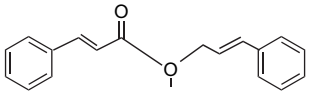
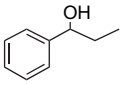
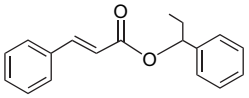
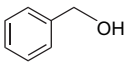
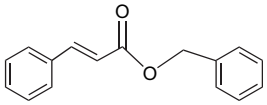
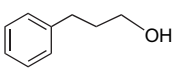
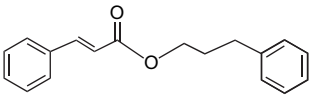
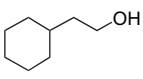
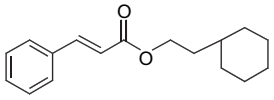
Table 3. Effect of heterogeneous catalyst on the synthesis of methyl cinnamate from cinnamaldehyde[a]



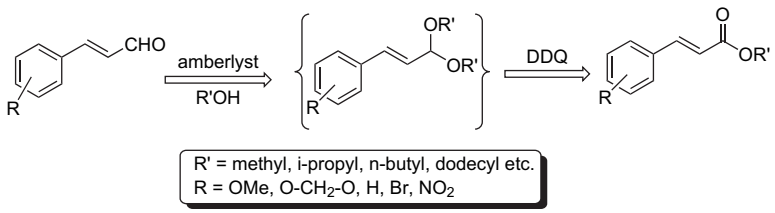
Support	Reaction time (min)	Product yield (%)
Amberlyst-15	30	96
Alumina (neutral)	120	94
Amberlyte IR-120	40	93
Alumina (acidic)	50	89
Silica gel	120	85

[a] The reaction was carried out under microwave fitted with Dean–Stark apparatus using **1a** (37.5 mmol), DDQ (56.3 mmol), MeOH (4–5 mL), toluene (20–25 mL) and heterogeneous catalyst (0.1–0.2 g).

Table 4. Effect of nature of alcohols on the synthesis of (*E*)-cinnamic esters from cinnamaldehyde

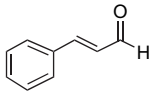
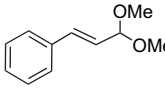
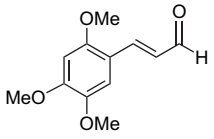
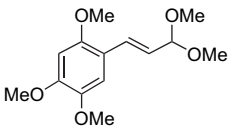
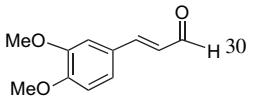
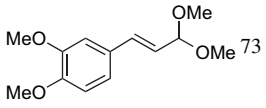
Entry	Alcohol	Reaction time (min)	Product	Yield (%)	Reference
1	MeOH	30		96	4i,25j
2	EtOH	35		89	4h,25h
3	*n*-BuOH	30		92	25g
4	$CH_3(CH_2)_6CH_2OH$	40		91	25l
5	$CH_3(CH_2)_{10}CH_2OH$	40		90	26
6	^{i}Pr-OH	60		31	25d
7	^{i}Amyl-OH	40		79	25a
8	^{t}Bu-OH	120		0	4k
9	$(CH_2OH)_2$	60		35	25k
10	$(OMe)CH_2CH_2OH$	30		92	25k,26
11		40		5[a]	2a
12		40		0[a]	26
13		40		0[a]	26
14		40		89	2a
15		40		88[b]	—

[a] Instead of expected esters, the alcohols (entries 11–13) were oxidized to cinnamaldehyde, 1-phenyl-l-propanone and benzaldehyde, respectively.
[b] Synthetic procedure and spectral data of this new compound is given in Section 4.



Scheme 2.

Table 5. Trapping of intermediate from cinnamaldehydes[a]

Entry	Substrate	Reaction time (min)	Product	Yield (%)
1		30		71
2		30		73
3		30		73

[a] Reaction conditions: cinnamaldehyde (37.5 mmol), Amberlyst-15 (0.2 g), MeOH (2–3 mL) and toluene (10–15 mL) refluxed under microwave fitted with Dean–Stark. Reaction mixture is filtered, concentrated, directly loaded on a neutral alumina column and eluted with toluene. Product analysed on the basis of NMR.

Mechanistically, the reaction is believed to occur by an Amberlyst-promoted attack of alcohol on cinnamaldehyde to form the hemiacetal,[14] which subsequently gets oxidized with DDQ to form the cinnamic ester (Scheme 2). To reinforce the above postulate, cinnamaldehydes were reacted with MeOH in Amberlyst-15 alone, i.e., without DDQ and the product was confirmed to be hemiacetal[14] (Table 5) on the basis of NMR investigations. It was also noticed that the addition of DDQ after formation of intermediate hemiacetal in the reaction mixture provided the required (*E*)-cinnamic ester. Overall, the process not only provides the esters[25,26] (Tables 1 and 4) in high yield after just passing the crude mixture through a bed of alumina, but also gives an opportunity to reuse the catalyst and oxidant.[27]

3. Conclusion

In conclusion, heterogeneously catalyzed oxidation of substituted cinnamaldehydes or cinnamyl alcohols with DDQ is a clean and atom economical method and to the best of our knowledge, reported for the first time for the chemoselective synthesis of various (*E*)-cinnamic esters in high yield in an energy efficient manner without either using strong acids or hazardous reagents. Moreover, the pronounced chemoselectivity of this method towards α,β-unsaturated aromatic aldehydes over aromatic or aliphatic aldehydes has the potential to eliminate the tedious protection–deprotection sequences in complex natural product synthesis. Further, efforts to extend the scope of the developed protocol are currently underway.

4. Experimental section

4.1. General remarks

Melting points were determined with a Mettler FP80 micromelting point apparatus and are uncorrected. Column chromatography was performed on neutral alumina. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. CEM Discover© focused microwave (2450 MHz, 300 W) was used wherever mentioned.

4.2. General procedure for the chemoselective esterification of α,β-unsaturated cinnamaldehydes and cinnamyl alcohols (Tables 1 and 4)

The synthesis of 2′-cyclohexylethyl 3-phenylpropanoate (Table 4, entry 15) as given below is representative of the general procedure employed for the synthesis of (*E*)-cinnamic esters (Tables 1 and 4). The mixture containing cinnamaldehyde (37.5 mmol), DDQ (56.3 mmol), 2-cyclohexyl-ethanol (75 mmol) and toluene (10–15 mL) was taken in a round-bottom flask and heterogeneous catalyst (Amberlyst-15, 0.1–0.2 g) was added to it. The flask was shaken well and irradiated under focused monomode microwave system (100 W, 110 °C) fitted with Dean–Stark apparatus for 40 min. Thereafter, the precipitated $DDQH_2$ and Amberlyst-15 were filtered. The filtrate was passed over a bed of neutral alumina column and eluted with 2–5% mixture of methanol in toluene. The obtained organic layer after evaporation under vacuum provided 8.51 g (88%) of 2′-cyclohexylethyl 3-phenylpropanoate as viscous liquid; IR (KBr) 1685 (C=O); ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, d, J=15.64 Hz), 7.46 (2H, m), 7.30 (3H, m), 6.40 (1H, d, J=15.64 Hz), 4.20 (2H, t, J=6.86 Hz), 1.70 (4H, m), 1.57 (3H, m), 1.35 (1H, m), 1.20 (3H, m), 0.94 (2H, m); ^{13}C NMR ($CDCl_3$) δ 167.1, 144.5, 134.5, 130.2, 128.8, 128.0, 118.3, 62.8, 36.1, 34.6, 33.2, 26.5 and 26.2. HREIMS data: m/z $[M+H]^+$ for $C_{17}H_{23}O_2$ calculated 259.3698, observed 259.3664. The spectral data and physical properties of all other (*E*)-cinnamic esters (Tables 1 and 4) were found matching with the reported values[2,4,25,26] (see the Supplementary data for details).

In the above reaction, the filtered $DDQH_2$ and Amberlyst-15 were dissolved in alcohol (methanol/ethanol), which led to the complete separation of $DDQH_2$ and Amberlyst-15. The recovered Amberlyst-15 was consecutively reused three

times with a minimum variation in the yield of cinnamic esters. Regeneration of DDQ from $DDQH_2$ has been reported earlier.[27] In addition, the solvent mixture (alcohol and toluene) recovered from reaction mixture or after column purification was found suitable for the next batch as our protocol did not require aqueous work up.

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Supplementary data

Supporting information available: spectral data of some representative (*E*)-cinnamic esters. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.11.011.

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