Novel Deoxygenation Reaction of Epoxides by Indium

Mohan Mahesh,[†] John A. Murphy,[*,†] and Hans Peter Wessel[‡]

Department of Pure and Applied Chemistry, University of Strathclyde, 295, Cathedral Street,
Glasgow G1 1XL, UK, and Pharma Research, Discovery Chemistry, F. Hoffmann-La Roche, Ltd.,
Basel, CH-4070, Switzerland

john.murphy@strath.ac.uk

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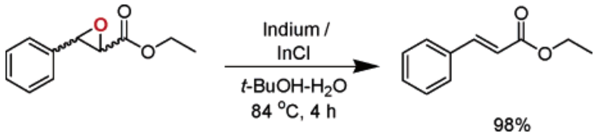

A novel, mild, ecofriendly protocol for the deoxygenation of epoxides to alkenes using indium metal and indium(I) chloride or ammonium chloride in alcohol has been developed. It was necessary for the presence of good radical-stabilizing groups adjacent to the oxirane ring for the deoxygenation reaction to occur. It is proposed that this reaction occurs through an SET process with indium as an electron donor.

Introduction

Electron-transfer reactions mediated by indium have attracted the attention of synthetic chemists due to its low first ionization potential[1] of 5.79 eV, which is lower than many reducing metals such as aluminum[2] (5.98 eV), tin[2] (7.34 eV), magnesium[2] (7.65 eV), and zinc[2] (9.39 eV) and close to that of alkali metals[2,3a] such as sodium (5.12 eV) and lithium (5.39 eV). Having such a low ionization potential makes indium attractive for conducting reductions. This is particularly so because it is so much easier to handle than alkali metals; for example, the metal remains unaffected by air or oxygen at ordinary temperatures and is practically unaffected by water even at high temperatures[1,3a] and very resistant to alkaline conditions.[3a] Thus, there is a practical convenience of performing indium-mediated reactions in water or moisture-containing solvents.[1,3a,b] It is noteworthy that indium metal apparently has no significant toxicity[1,3a] and has found considerable utility in dental alloys.[1]

Indium metal has been effectively used in modern organic synthesis particularly in a wide range of reduction reactions.[1−35] In general, these are thought to proceed through facile single-electron transfer from metallic indium to form an indium(I) species, although precise intermediates have not been established in most cases. The first electron would certainly be transferred with much greater ease than subsequent electrons, as

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[†] University of Strathclyde.

[‡] F. Hoffmann-La Roche, Ltd.

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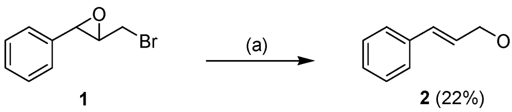
the second ionization potential for indium is much higher (18.86 eV). Indium metal has been successfully studied as a single-electron transfer (SET) radical initiator in tandem radical addition/cyclization/trapping reactions in aqueous media or in alcohol solvents,[36] and recently, indium−iodine-mediated reductive radical cyclization of iodoalkenes and iodoalkynes has been reported.[37] Whereas indium metal has been used for so many reduction reactions, it has not been exploited in the reduction of epoxides. Herein we report a novel deoxygenation reaction of epoxides to alkenes mediated by electron transfer from indium.

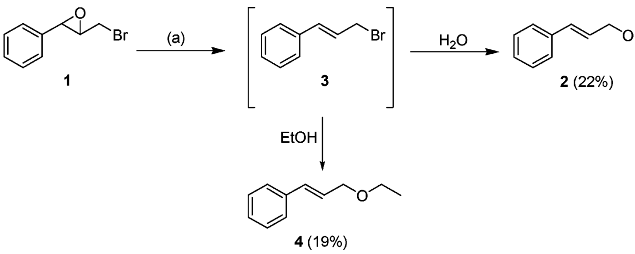
Alkenes are very important in organic synthesis (metathesis, pericyclic reactions, Heck reaction, dihydroxylation, etc.). With a plethora of protective groups available for various types of functional groups, it is rather surprising that no practical protecting groups have been developed for double bonds. Epoxidation can be used as a means of protecting double bonds; however, the successful implementation of this strategy would largely depend on the effective deoxygenation of epoxides back to alkenes. In efforts to explore a more facile and environment-friendly protocol for the deoxygenation of epoxides, we developed a mild methodology of deoxygenation of epoxides with good radical-stabilizing groups adjacent to the oxirane ring, using indium metal and indium(I) chloride or ammonium chloride in alcohol as a solvent. This reaction is a good complement to known methods of deoxygenation of epoxides,[38−54] showing exquisite levels of chemoselectivity for epoxides bearing radical-stabilizing groups on the epoxide carbons.

SCHEME 1[a]



[a] Reagents and conditions: (a) indium (2 equiv), THF−H_2O (1:1), rt, 48 h, 22%.

SCHEME 2[a]



[a] Reagents and conditions: (a) indium (2.7 equiv), NH_4Cl (2 equiv), EtOH, 78 °C, 24 h, 22% (**2**), 19% (**4**).

Results and Discussion

The deoxygenation of epoxides by indium metal was discovered in our hands when radical ring-opening reactions were attempted on 2-bromomethyl-3-phenyloxirane **1** with indium metal to yield cinnamyl alcohol in 22% yield (Scheme 1).

When the reaction was repeated using indium and ammonium chloride using ethanol as the solvent, cinnamyl alcohol **2** was obtained in 22% yield along with the 1-[(*E*)-3-ethoxyprop-1-enyl]benzene **4** in 19% yield (Scheme 2).

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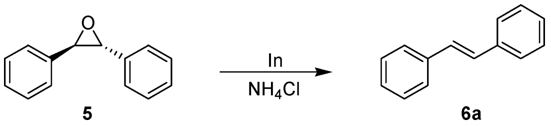
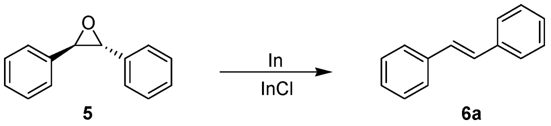
TABLE 1. Deoxygenation of *trans*-Stilbene Oxide Using Indium/NH_4Cl



entry	equiv of indium	salt used/equiv	solvent	time	temp (°C)	isolated yield (%)	
						6a	**5** (recovered)
i	7.0	NH_4Cl (2 equiv)	ethanol (98%)	96 h	80	92	–
ii[a]	–	NH_4Cl (2 equiv)	ethanol (98%)	96 h	80	–	99
iii	7.0	–	THF–H_2O (1:1)	96 h	25	5	92
iv	7.0	NH_4Cl (2 equiv)	acetone	96 h	56	0	70
v	7.0	NH_4Cl (2 equiv)	THF	96 h	65	5	87

[a] Control reaction performed in the absence of indium metal.

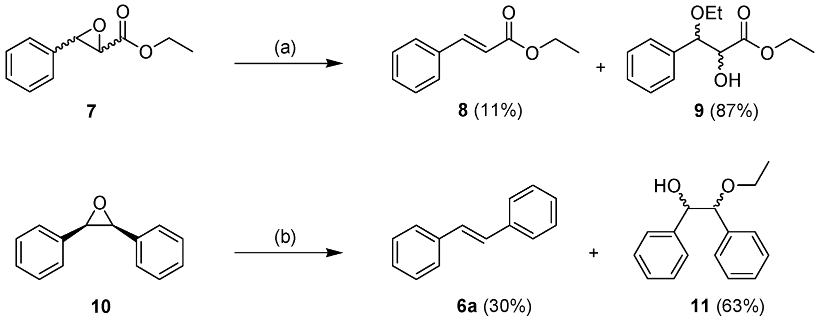
TABLE 2. Deoxygenation of *trans*-Stilbene Oxide Using Indium/InCl



entry	equiv of indium	salt used/equiv	solvent	time	temp (°C)	isolated yield of **6a** (%)
i	2.5	InCl (2 equiv)	ethanol (98%)	6 h	80	80
ii[a]	0	InCl (2 equiv)	ethanol (98%)	6 h	80	0
iii	2.5	InCl (2 equiv)	DMF	6 h	120	7
iv	2.5	InCl (2 equiv)	THF (anhydrous)	6 h	65	0
v	2.5	InCl (2 equiv)	1,2-dimethoxyethane	6 h	85	0
vi	2.5	InCl (2 equiv)	*t*-BuOH (anhydrous)	6 h	83	0
vii	2.5	InCl (2 equiv)	CF_3CH_2OH	6 h	80	0
viii	2.5	InCl (2 equiv)	$(CF_3)_2CHOH$	6 h	59	0
ix	2.5	InCl (2 equiv)	acetonitrile	6 h	82	0

[a] Control reaction performed in the absence of indium metal.

SCHEME 3[a]



[a] Reagents and conditions: (a) indium (3.5 equiv), InCl (1.5 equiv), EtOH, 80 °C, 7 h, 11% (**8**), 87% (**9**); (b) indium (3.5 equiv), InCl (1.5 equiv), EtOH, 80 °C, 8 h, 30% (**6a**), 63% (**11**).

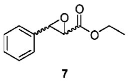
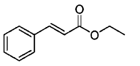
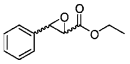
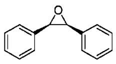
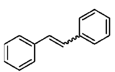
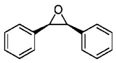
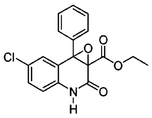
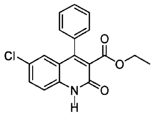
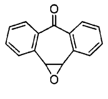
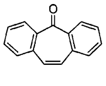
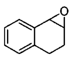
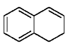
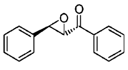
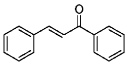
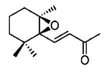
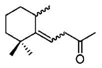
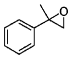
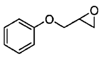
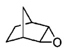
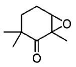
We proposed that the cinnamyl alcohol **2** and unsaturated ether **4** were derived from cinnamyl bromide, which was formed as a result of deoxygenation of the epoxide **1** by indium. These preliminary results invited more investigation of the deoxygenation of epoxides.

The experimental conditions for this deoxygenation reaction were studied in detail using *trans*-stilbene oxide **5** as the standard epoxide. The preliminary results of deoxygenation of *trans*-stilbene oxide **5** to *trans*-stilbene **6a** using indium/NH_4Cl are summarized in Table 1.

At this stage, the role of the ammonium chloride in our reactions was questioned. One role would involve activation of the epoxide (lowering of the energies of the C–O σ^* orbitals) through hydrogen bonding to the epoxide. An alternative means of activating the epoxide would be by Lewis acid activation using an indium(I) species formed by the oxidation of indium metal through a single electron-transfer mechanism. To probe this possibility, the reaction was repeated using indium/indium(I) chloride, and encouraging results were obtained. Utilization of indium(I) chloride, instead of NH_4Cl, considerably decreased not only the total time of the reaction from 96 to 6 h but also the number of equivalents of indium metal required from 7 to 2.5 equiv [compare entry i of Tables 1 and 2]. The deoxygenation reaction of *trans*-stilbene oxide was studied using indium/indium(I) chloride in different solvents, and the results are summarized in Table 2.

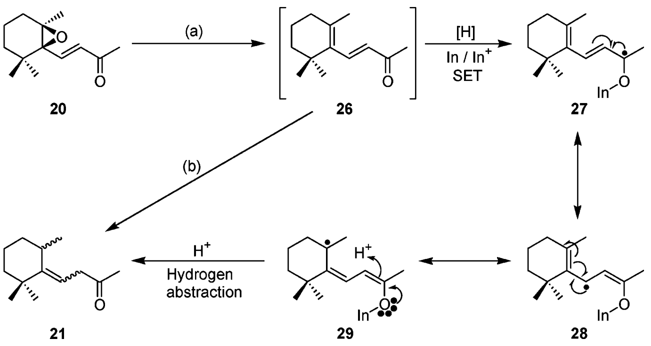
Ethanol was the most effective solvent in the above reaction; however, it was not effective for the deoxygen-

TABLE 3. Deoxygenation Reaction of Epoxides by Indium

entry	epoxides	alkene(s) obtained	equiv of indium / salt used / solvent	time / temperature	E/Z^{b}	isolated yield (%)
i	 **7** (*cis* and *trans*)	 **8**	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	4 h, 84 °C	1:0	98
ii[a]	 **7**	no alkene	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH (anhydrous)	4 h, 84 °C	-	-
iii	 **10**	 **6**	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	5 h, 84 °C	3:1	84
iv[a]	 **10**	no alkene	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH (anhydrous)	5 h, 84 °C	-	-
v	 **12**	 **13**	indium (4 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	24 h, 84 °C	-	94
vi	 **14**	 **15**	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	6 h, 84 °C	-	81
vii	 **16**	 **17**	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	2.5 h, 70 °C	-	69
viii	 **18**	 **19**	indium (3 equiv) NH$_4$Cl (2.0 equiv) EtOH (98%)	4 h, 80 °C	1:0	51
ix	 **20**	 **21**	indium (4 equiv) InCl (2 equiv) *t*-BuOH-H$_2$O (24:1)	30 h, 84 °C	1:0.7[c]	81
x	 **22**	no alkene	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	4 h, 84 °C	-	-
xi	 **23**	no alkene	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	8 h, 84 °C	-	-
xii	 **24**	no alkene	indium (3 equiv) NH$_4$Cl (2 equiv) EtOH (98%)	5 h, 80 °C	-	-
xiii	 **25**	no alkene	indium (3 equiv) InCl (1.5 equiv) *t*-BuOH-H$_2$O (24:1)	12 h, 84 °C	-	-

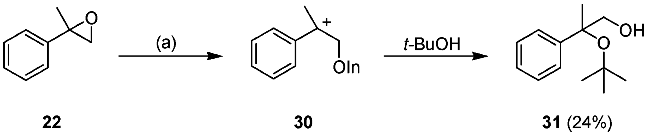
[a] Reactions performed in anhydrous *tert*-butyl alcohol. [b] All E:Z ratios were determined from the peak area ratio of the ^{1}H NMR spectral analysis. [c] The stereochemistry of the alkene **21** were determined by one-dimensional ^{1}H NOE, two-dimensional ^{1}H NOESY, and DQFCOSY NMR experiments

SCHEME 4[a]



[a] Reagents and conditions: (a) indium (4 equiv), InCl (2 equiv), t-BuOH−H_2O (24:1), 84 °C, 30 h, 81% (E:Z = 1:0.7); (b) indium (4 equiv), InCl (2 equiv), t-BuOH−H_2O (24:1), 84 °C, 30 h, 84% (E:Z = 1:0.8).

SCHEME 5[a]



[a] Reagents and conditions: (a) indium (3 equiv), InCl (1.5 equiv), t-BuOH−H_2O (24:1), 84 °C, 4 h, 24%.

ation reactions of some epoxides that were sensitive to nucleophilic attack due to the competing ring-opening reaction by ethanol on the oxirane ring (Scheme 3).

However, this problem was overcome by using less nucleophilic *tert*-butyl alcohol−H_2O (24:1) as the solvent system (Table 3). It is noteworthy that none of the deoxygenation reactions worked in anhydrous *tert*-butyl alcohol, thereby indicating the importance of minute quantities of water for the deoxygenation in that solvent (Table 3).

Oxirane **20** underwent smooth deoxygenation to afford the alkene **21** in excellent 81% yield (Table 3). The formation of the alkene **21** can be explained via the reduction of the expected dienone intermediate **26** by indium metal (Scheme 4). In an independent experiment, when β-ionone **26** was treated with identical conditions of indium/indium(I) chloride in *tert*-butyl alcohol−H_2O, it resulted in the formation of the same alkene **21** in a comparable yield of 84% with similar E:Z ratio (Scheme 4).

The deoxygenation of the terminal epoxide 2-methyl-2-phenyloxirane **22** was not successful due to the competing indium(I) chloride-promoted ring-opening reaction of epoxide via the stable tertiary carbocation intermediate **30**. Eventually the alcohol **31** was isolated as the major product from the reaction in 24% yield (Scheme 5).

Table 3 shows that the presence of an activating group (phenyl or vinyl) adjacent to the oxirane ring was necessary for the deoxygenation reaction. Epoxides without the activating group adjacent to the oxirane ring did not undergo deoxygenation.

Although the exact mechanism for the deoxygenation is not known at this stage, it may be proposed that the first step involves a single electron-transfer from the indium metal to the low-lying σ^* orbital of the C−O bond, giving rise to a radical **34**, which can eventually break to the alkene following any of the proposed mechanisms **A**, **B**, or **C** (Scheme 6).

Conclusion and Scope. We have developed a mild and effective methodology to deoxygenate epoxides using indium metal under mild conditions. The presence of a radical-stabilizing group adjacent to the oxirane ring was necessary for the deoxygenation. The reaction requires protic solvents such as ethanol or methanol or t-butanol and a salt like ammonium chloride or indium(I) chloride for the deoxygenation. The presence of minute quantities of water in the solvent is necessary for the deoxygenation. For sensitive aryl epoxides that are susceptible to a nucleophilic attack of alcohols, *tert*-butyl alcohol−H_2O is a better solvent system.

Investigation of deoxygenation of epoxides with different activating groups adjacent to the oxirane ring and mechanistic aspects of the reaction is currently in progress.

Experimental Section

Deoxygenation of Epoxides: General Procedure A [Deoxygenation of *trans*-Stilbene Oxide (5) Using Indium/NH_4Cl in Ethanol as Solvent]. *trans*-Stilbene oxide **5** (0.3925 g, 2.0 mmol, 1.00 equiv) was dissolved in 98% ethanol (20 mL), and indium metal powder (0.459 g, 4.0 mmol, 2.00 equiv), followed by ammonium chloride (0.214 g, 4.0 mmol, 2.0 equiv), was added to the solution. The reaction mixture was heated to reflux at 80 °C under a nitrogen atmosphere for 24 h. After 24 h, an additional quantity of indium metal powder (1.148 g, 10.0 mmol, 5.00 equiv) was added to the reaction mixture, and reflux was continued for a further 72 h (96 h in total) at 80 °C. The reaction mixture was diluted with diethyl ether (100 mL), and the white-grey precipitate was filtered through Celite. The filtrate was washed with saturated brine solution (3 × 100 mL), and the organic layer was separated. The organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness under reduced pressure to obtain *trans*-stilbene **6a** (0.331 g, 92%) as a white solid: mp 123−124 °C (lit.[55] 123−124 °C) [found (EI) $M^{+\bullet}$ 180.0931, $C_{14}H_{12}$ requires M 180.0934]; IR (KBr) 3078, 3060, 3020, 1598, 1577, 1495, 1451, 1332, 1300, 1220, 1184, 1155, 1072, 1029, 983, 961, 909, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (s, 2H), 7.22−7.29 (m, 2H), 7.36−7.39 (m, 4H), 7.49−7.53 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 127.0 (CH), 128.1 (CH), 129.1 (CH), 129.2 (CH), 137.8 (C); m/z (EI) 180 ($M^{+\bullet}$, 97%), 179 (100), 178 (70), 176 (14), 165 (52), 152 (16), 151 (7), 139 (5), 126 (4), 115 (6), 102 (10), 89 (18), 77 (10), 76 (14), 63 (9), 51 (11). The spectroscopic data of *trans*-stilbene **6a** were identical with those of an authentic commercial sample and consistent with those reported in the literature.[56]

General Procedure B [Deoxygenation of *trans*-Stilbene Oxide Using Indium/InCl in Ethanol as Solvent]. Indium metal powder (0.287 g, 2.5 mmol, 2.50 equiv) and indium(I) chloride (0.301 g, 2.0 mmol, 2.00 equiv) were added to a stirred solution of *trans*-stilbene oxide **5** (0.196 g, 1.0 mmol, 1.00 equiv) in 98% ethanol (20 mL) at rt. The reaction mixture was heated to reflux at 80 °C and stirred vigorously under an argon atmosphere for 6 h. A white turbidity appeared in the reaction mixture initially that later turned to a white-grey precipitate. When the reaction was complete, the reaction mixture was cooled to rt and diluted with diethyl ether (100

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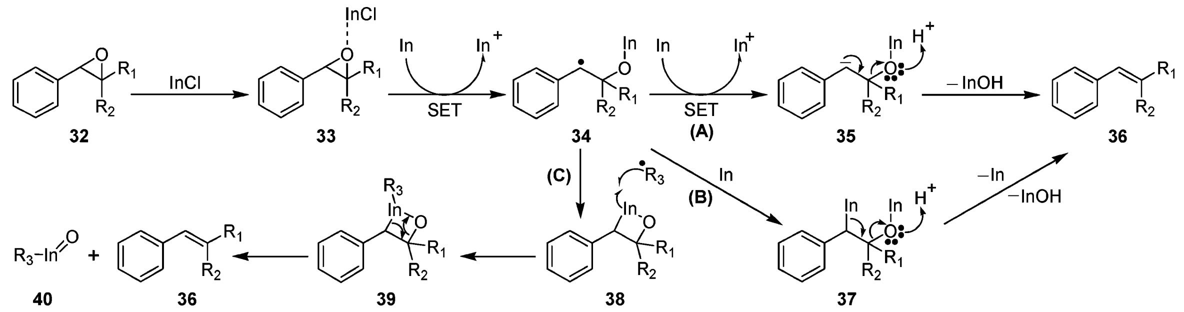
SCHEME 6



mL), and the precipitate was filtered through Celite using a sintered funnel. The filtrate was evaporated to dryness under reduced pressure to obtain a white semisolid that was redissolved in diethyl ether (100 mL) and washed with saturated brine solution (3 × 100 mL). The organic phase was separated using a separating funnel, dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to obtain a white semisolid. This was purified by flash chromatography on silica gel [ethyl acetate/*n*-heptane = 1:49] to afford *trans*-stilbene **6a** (0.144 g, 80%) as white crystals, mp 123−124 °C (lit.[55] mp 123−124 °C). The spectroscopic data of the *trans*-stilbene **6a** were identical with those of the same compound reported earlier and those reported in the literature.[56]

General Procedure C [Deoxygenation of Ethyl-(±)-3-phenylglycidate (7) by Indium/InCl Using *tert*-Butyl Alcohol−Water as the Solvent]. Indium metal powder (0.172 g, 1.5 mol, 3.00 equiv), indium(I) chloride (0.113 g, 0.75 mmol, 1.50 equiv), and deionized water (0.2 mL) were added to a solution of ethyl-(±)-3-phenylglycidate **7** (0.1045 g of a 92% mixture of cis and trans, 0.5 mmol, 1.00 equiv) in *tert*-butyl alcohol (4.8 mL) at 30 °C. The reaction mixture was heated to reflux at 84 °C while stirring vigorously under an argon atmosphere for 4 h. A white turbidity appeared in the reaction mixture initially, which later turned to a deep white-grey precipitate. When the reaction was complete, the reaction mixture was cooled to rt and filtered through Celite with ethyl acetate (3 × 25 mL). The filtrate was concentrated under reduced pressure to yield a colorless oil that was redissolved in ethyl acetate (75 mL) and washed with saturated brine solution (3 × 75 mL). The organic phase was separated using a separating funnel, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain a colorless oil. The crude material was purified by flash chromatography on silica gel [ethyl acetate/petroleum ether = 1:9] to afford *trans*-ethyl cinnamate **8** (0.086 g, 98%) as a colorless oil: IR (neat) 3062, 3029, 2982, 1714, 1639, 1579, 1496, 1450, 1393, 1367, 1311, 1270, 1203, 1176, 1096, 1072, 1039, 980, 865, 839, 768, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 4.28 (q, J = 7.1 Hz, 2H), 6.45 (d, J = 16.0 Hz, 1H), 7.33−7.43 (m, 3H), 7.49−7.56 (m, 2H), 7.70 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100.61 MHz, $CDCl_3$) δ 14.8 (CH_3), 61.0 (CH_2), 118.8 (CH), 128.6 (CH), 129.4 (CH), 130.7 (CH), 135.0 (C), 145.1 (CH), 167.5 (C); GC-MS retention time 13.20 min, *m/z* (EI) 176 ($M^{+\bullet}$, 37%), 148 (24), 147 (23), 131 (100), 103 (44), 91 (4), 77 (16), 51 (8). The spectroscopic data of the *trans*-ethyl cinnamate **8** were consistent with those in the literature.[57]

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Supporting Information Available: Experimental procedures and spectroscopic data for compounds not included in the Experimental Section, as well as ^{1}H and ^{13}C NMR spectra for compounds **1**, **2**, **4**, **6a**, **8**, **9**, **11**−**13**, **15**−**17**, **19**−**22**, **25**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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