Cooperative Zinc/Catalytic Indium System for the Stereoselective Sequential Synthesis of (E)-1,3-Dienes from Carbonyl Compounds

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ARTICLE

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Herein we describe a cooperative zinc/indium system for the stereoselective synthesis of highly functionalized (*E*)-1,3-dienes through the sequential allylation/elimination reaction of aldehydes and ketones with 1,3-dichloropropene. This methodology has as the main advantages a broad substrate scope, mild conditions an operationally easy and simple procedure.

Introduction

1,3-Diene motif is one of the most important structural units in organic chemistry,[1] on account of its ubiquitous presence in natural products of biological relevance such as arachidonic acids,[2] retinoids,[3] antibiotics,[4] and marine natural products.[5] In addition, 1,3-dienes are valuable intermediates in the synthesis of diverse functionalities, such as carbacycles and heterocycles,[6] cyclopropanes[7] or β-lactams.[8] As a consequence, considerable efforts has been made in the past few years in the development of methods for their stereoselective synthesis.[9]

Many of the existing methods for the synthesis of dienes are based on transition metal catalyzed reactions, including bond reorganization of enyne substrates,[10] olefin methathesis,[11] sp^2-sp^2 cross-coupling of two suitably functionalized olefinic moieties,[12] rearrangement of allenes[13] and diene isomerization.[14] However, the use of expensive metal catalysts, multiple prefunctionalization steps and harsh reaction conditions, limit their applicability.

For total synthesis, the ideal scenario would be the installation of the 1,3-diene moiety in a single step with high stereoselectivity. In this regard, the direct synthesis of the 1,3-diene *via* olefination of carbonyl groups is a very attractive alternative, which have enjoyed considerable attention. Diene formation through Wittig,[15] Wittig-Horner,[16] Horner–Wadsworth–Emmons (HWE),[17] and Julia–Kocienski[18] olefination reactions reportedly produce dienes in moderate to good yields albeit with moderate and substrate-dependant (*E*/*Z*)-selectivity. Moreover, the use of γ-silyl-substituted allylmetal reagents, under Peterson conditions, afforded dienes in high *E*-selectivity but usually lack generality and require strict reaction conditions and/or the use of highly toxic and complex reagents, so there is still much room for improvement.[19-25]

In the search for a simple and economical protocol for the stereoselective synthesis of 1,3-dienes, we have recently reported the indium-based preparation of (*E*)-1,3-dienes by the means of the chloroallylation of aldehydes followed by β-elimination of the resulting chlorohydrines.[26]

Indium-mediated organic reactions have elicited considerable interest in the past few years.[27] The usefulness of indium in chemistry is related to its very low first ionization energy (5.79 eV), which makes it an ideal candidate to promote single-electron transfer (SET) processes. [28] This property, together with its relatively low toxicity, easy handling and stability to oxygen and water, prompted exhaustive studies focused on various indium-mediated organic transformations, including C-C forming reactions, such as allylations,[29] propargylations,[30] alkynylations,[31] Reformatsky reactions[32] cyclopropanation reactions,[33] Henry-type nitronate additions,[34] β-eliminations[35] and dehalogenations.[36]

Despite its low toxicity, environmental benefits and favourable effects on chemical transformations, the use of indium as reagent for synthetic transformations have diminished in the past few years, mainly due to its increased cost. In nature indium is quite rare, and nearly always found as a trace element. However, indium is vital to the world's economy, as it is widely used for LCD's (liquid crystal displays) in touch screens, flat screen TVs and solar panels. The growing demand had pushed indium into the endangered elements list and increased the prices considerably in recent years. In this context, the use of stoichiometric amounts of indium for chemical reactions is highly discouraged.

In recent years, an important effort has been made to reduce the amount of indium used in indium-promoted reactions. In those processes, most of the indium was substituted by other cheaper metals such as aluminium, zinc or manganese, proving that the electroreductive regeneration of low-valent indium could be achieved and thus drastically reducing the costs.[37]

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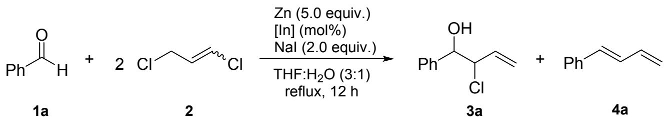
Electronic Supplementary Information (ESI) available: [^{1}H (300 MHz), and ^{13}C (75 MHz) NMR for dienes **4** and **6**]. See DOI: 10.1039/x0xx00000x

Herein we report a simple, straightforward, cost-efficient procedure for the stereoselective preparation of (*E*)-1,3-dienes from different carbonyl compounds in a single step using catalytic indium in the presence of zinc.

Results and Discussion

In order to determine the feasibility of the sequential allylation/reductive elimination process, the reaction of benzaldehyde **1a** and 1,3-dichloropropene was used as the model under various conditions.

Table 1. Studies on the synthesis of (*E*)-1-phenyl-1,3-butadiene.[a]



Entry	[In] (mol%)	**3a/4a**	*E/Z*[b]	Yield (%)[c]
1[d]	In (25)	87/13	*n.d.*	12
2	In (25)	14/86	>98/2	83
3[e]	In (25)	30/70	96/4	62
4[f]	In (25)	32/68	*n.d.*	38
5	-	24/76	>98/2	59
6[g]	In (100)	>98/2	-	-
7[h]	In (25)	25/75	>98/2	62
8	In (10)	26/74	>98/2	51
9[i]	In (25)	29/71	*n.d.*	36
10	$InCl_3$ (25)	14/86	>98/2	83
11	$InCl_3$ (10)	15/85	>98/2	81
12	$InCl_3$ (5.0)	21/79	>98/2	70

[a] Unless otherwise noted, all reactions were conducted at 5.0 mmol Zn, 2.0 mmol NaI, THF:H_2O (3:1), and reflux. [b] Determined by ^1H NMR (300 MHz) analysis of the crude reaction mixtures. [c] Isolated yield of compound **4a** after flash column chromatography based on compounds **1a**. [d] Reaction carried out at r.t. [e] Reaction carried out in neat THF. [f] Reaction carried out in THF:H_2O (1:3). [g] Reaction carried out in the absence of Zn. [h] Reaction carried out in the absence of NaI. [i] 2.5 mmol of Zn were used.

As shown in table 1, treatment of aldehyde **1a** (1.0 mmol) with dichloropropene (2.0 mmol), substoichiometric indium powder (25% mol) and zinc dust (5.0 mmol) in the presence of sodium iodide (2.0 mmol) in a mixture of THF and H_2O (3:1) at room temperature for 12 hours the major product of the reaction was the chlorohydrin **3a** (Table 1, entry 1) On contrary, when the reaction was performed at reflux for 12 hours led to the formation of (*E*)-1,3-diene **4a** in good yield and excellent *E*-stereoselectivity (Table 1, entry 2).

Changing the solvent to neat THF as solvent led to poorer results, both in terms of yield and selectivity (Table 1, entry 3). Moreover, the use of a mixture of THF:H_2O (1:3), the yield of the desired diene **4a** was considerably lower (Table 1, entry 4) when compared with the result showed in entry 1. On the other hand, in the absence of indium the yield of the diene is moderate (Table 1, entry 5) and, the presence of stoichiometric indium and absence of zinc, afforded the chlorohydrine **3a** as the major product (Table 1, entry 6).The presence of sodium iodide as additive is also essential; in its absence, the reaction was found to proceed sluggishly (Table 1, entry 7). It is evident that the iodide plays the role of activating the allyl chloride by converting it to more reactive allyl iodide *via* Finkelstein-type reaction pathway.[38]

It is also noteworthy that lowering the amounts of either indium or zinc resulted in decreased yields of the diene product (Table 1, entries 8 and 9).

The use of substoichiometric indium is in agreement with a catalytic cycle in which In^0 would be regenerated from In^{+3} by zinc metal, which possess a higher standard reduction potential.[39] If such catalytic cycle were operative, it is expected that indium salts would perform as effectively as indium metal. In order to verify this hypothesis, we replaced the indium powder for indium trichloride, the cheapest In^{+3} salt. Thus, a mixture of benzaldehyde **1a** (1.0 mmol), dichloropropene (2.0 mmol), zinc powder (5.0 mmol), indium trichloride (25 mol%), and sodium iodide (2.0 mmol) in THF:H_2O (3:1) was refluxed for 12 h. We were delighted to find that $InCl_3$ conducted to the formation of the corresponding diene **4a** with good yield similarly to indium metal, thus confirming that In^{+3} is reduced *in situ* to In^0 (Table 1, entry 10). Interestingly, the reaction performs better in the presence of $InCl_3$, allowing the use of a 10 mol% of catalyst (Table 1, entry 11). This result can be explained by the *in situ* formation of a more reactive form of In^0 than commercially available indium metal.[40] Lowering the catalyst loading to 5% resulted in a decrease of the yield of desired diene **4a** (Table 1, entry 12).

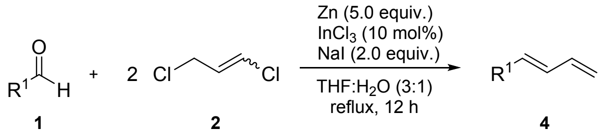
Based on the above results, the optimal reaction conditions were used to explore the scope of this protocol for synthesis of 1,3-dienes **4**. Thus, a mixture of diverse aldehydes **1** (1.0 mmol), zinc dust (5.0 mmol), indium trichloride (10 mol%) and sodium iodide (2.0 mmol) in THF:H_2O (3:1) was refluxed for 12 h (Table 2).

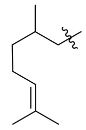
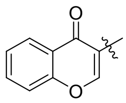
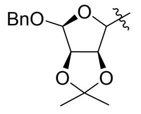
Under these conditions, aliphatic aldehydes (linear, cyclic, branched, and functionalized) **1b**-**f**, aromatic **1a,g-j** (electron rich or deficient), and conjugated **1k** were efficiently converted into the corresponding 1,3-dienes **4a-k** in good yields and excellent *E*-selectivity. The reaction was extended to the case of highly functionalized aldehydes, such as 3-formylchromone **4l** and sugar aldehyde **4m**. In both cases, the corresponding dienes were obtained in good yields and *E*-selectivity. In the case of sugar aldehyde **1m**, is noteworthy that the reaction occurred in absence of epimerization of any chiral centre. In general terms, several functional groups such as alkene, enone, alkoxy, halide, and ester were tolerated and remained unaffected under the present reaction conditions.

Dienes **4a**-**d**,**f**-**m** were previously synthetized and all the spectroscopic data match with those previously reported in the literature.[25,26,41,42] Diene **4e** was fully characterized through HRMS, IR and ^1H (300 MHz), and ^{13}C (75 MHz) NMR, analysis.

The satisfactory results obtained in the synthesis of 1-substituted-1,3-dienes from aldehydes prompted further studies on the usefulness of this methodology for the synthesis of (*E*)-1,1-substituted-1,3-dienes from ketones.

Table 2. Synthesis of (*E*)-1,3-dienes **4** derived from aldehydes **1**



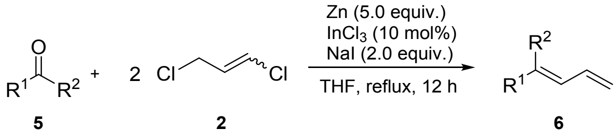
Entry	1	R^1	4	E/Z[a]	Yield (%)[b]
1	**1a**	Ph	**4a**	>98/2	83
2	**1b**	*n*-C_7H_{15}	**4b**	95/5	80
3	**1c**	*c*-C_6H_{11}	**4c**	>98/2	79
4	**1d**		**4d**	91/9	61
5	**1e**	$CH_3CH_2CH=CH(CH_2)_5$	**4e**	94/6	82
6	**1f**	$PhCH_2$	**4f**	85/15	63
7	**1g**	*p*-MeC_6H_4	**4g**	>98/2	90
8	**1h**	*p*-$MeOC_6H_4$	**4h**	>98/2	75
9	**1i**	*p*-ClC_6H_4	**4i**	>98/2	86
10	**1j**	*p*-$MeO_2CMeC_6H_4$	**4j**	>98/2	62
11	**1k**	(*E*)-PhCH=CH	**4k**	90/10	78
12	**1l**		**4l**	>98/2	85
13	**1m**		**4m**	93/7	63

[a] Determined by ^1H NMR (300 MHz) analysis of the crude reaction mixtures. [b] Isolated yield after flash column chromatography based on compounds **1**.

Thus, ketone **5a** was submitted to the above conditions; however, the corresponding 1,3-diene **6a** was isolated in very poor yield (Table 3, entry 1). Attempts to improve the yield by increasing the reaction time were unsuccessful (Table 3, entry 2). However, as a the main difference with the same process performed on aldehydes, when the reaction was carried out in anhydrous THF, 1,1-substituted-1,3-diene **6a** was isolated in good yield and *E*-selectivity (Table 3, entry 3). These reaction conditions were then applied to a series of ketones including aliphatic ketones (linear and cyclic) **5b,c**, benzylic ketone **5d,** aromatic ketones **5a,e-g** (electron rich or deficient), and with the conjugated chalcone **5h**. In all cases the corresponding dienes **6a-h** were obtained in moderate yields from moderate to good *E*-selectivity. In the case of **6d** (Table 3, entry 6) and analogously to that observed in the case of phenylacetaldehyde (Table 2, entry 6), a slight decrease on both, stereoselectivity and yield was observed which was attribute to the presence of acid benzylic protons. A similar trend was observed for ketone **5f** containing an electron-rich substituent.

Configuration of dienes **6a-g** were determined by comparison with the spectroscopic data reported in the literature.[12e,43-46] Diene **6h** was fully characterized through HRMS, IR, and ^1H (300 MHz), and ^{13}C (75 MHz) NMR analysis. The *E*-configuration was also confirmed and/or determined by using selective 1D NOE ^1H NMR experiments.

Table 3. Synthesis of (*E*)-1,3-dienes **6** derived from ketones **5**.

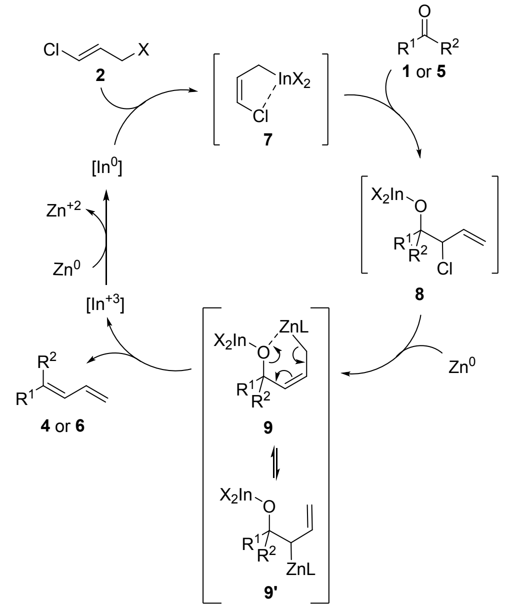


Entry	5	R^1	R^2	6	E/Z[a]	Yield (%)[b]
1[c]	**5a**	Ph	Me	**6a**	*n.d.*	5
2[d]	**5a**	Ph	Me	**6a**	*n.d.*	7
3	**5a**	Ph	Me	**6a**	92/8	64
4	**5b**	*n*-C_4H_9	*n*-C_4H_9	**6b**	-	60
5	**5c**	-$(CH_2)_5$-		**6c**	-	67
6	**5d**	$PhCH_2$	Me	**6d**	72/28	56
7	**5e**	*p*-MeC_6H_4	Me	**6e**	82/18	57
8	**5f**	*p*-$MeOC_6H_4$	Me	**6f**	70/30	38
9	**5g**	*p*-ClC_6H_4	Me	**6g**	81/19	51
10	**5h**	(*E*)-PhCH=CH	Ph	**6h**	82/18	45

[a] Determined by ^1H NMR (300 MHz) analysis of the crude reaction mixtures. [b] Isolated yield after flash column chromatography based on compounds **5**. [c] Reaction in THF:H_2O (3:1). [d] Reaction time 36 h.

To explain this transformation, we propose a sequential process in which a two step-wise metal-promoted transformation is involved. Concerning the first step, it is widely assumed that indium is the metal of choice for allylation protocols in aqueous media since the reaction usually proceed without the need of activation or addition of protic media, and the amount of side products due to reduction or coupling of carbonyl compounds is often minimal.[47] In this sense, the indium-promoted addition of dichloropropene to aldehydes **1** or ketones **5** would generate chloro alcoholates **8** (Scheme 1) *via* 1,2-addition of the anionic specie **7**[38,48] to the corresponding carbonyl compound.

In the second step of this process we propose a Zn-mediated metalation of the C-Cl bond on indium alcoholate **8**. This metalation would generate the metalotropic equilibrium **9-9'** which would be displaced to the **9**-form due to the chelation of the oxophilic Zn^{II} center with the oxygen atom.[49] This proposed six-membered ring could adopt two different half-chair conformations **9A** and **9B** (Figure 1). The most stabilized one would be **9A** in which R^1, as the group with the higher steric hindrance, adopts the equatorial position. We surmise an elimination process from intermediate **9A** (as depicted in Scheme 1) through an E1cB-type mechanism that would also explain the observed *E*-stereoselectivity.



Scheme 1. Proposed mechanism.

Once dienes **4** and **6** are generated, indium(III) species are then reduced in the presence of Zn to regenerate indium(0) that is again involved in the catalytic cycle to promote the above-mentioned indium-promoted addition of dichloropropene to carbonyl compounds.

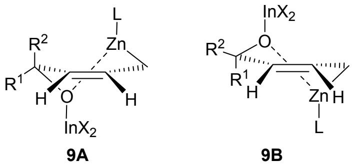
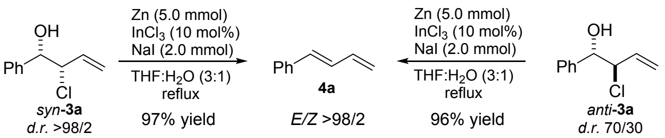


Figure 1. Proposed transition states.

In regard to the mechanism, the fact that the reaction promoted by stoichiometric indium (Table 1, entry 6) afforded only chlorohydrine **3a** rules out a mechanism based on the participation of the indium reactive species during the elimination process. Thus, zinc acts as both, as a secondary reductant and as the metalation agent in the sequential process. Related to this, the need of the indium salts is based on the yield of diene **4a** when compared with the same process in absence the indium. In this sense, the yield is moderate in the absence of indium as it is shown in Table 1 (entry 5). This fact is in accordance with the previous results described by Li.[50] Stereospecificity of this reaction was also studied. Thus, *syn*- and *anti*-chlorohydrines **3a** were prepared[38] and separated by flash chromatography on silica gel (only enriched fractions could be isolated) and treated at reflux of THF:H_2O (3:1) with $InCl_3$/Zn/NaI in (Scheme 2). In both cases, diene **4a** was stereoselectively obtained (*E*/*Z* >98/2) whether derived from *syn*-**3a** or *anti*-**3a** chlorohydrines. This experimental result suggested that this process took place in absence of stereospecificity but in a stereoselective manner. Moreover, a possible isomerization to the most stable *E*-diene under the reaction conditions has been discarded. Thus, when a *E/Z* 50/50 ratio of diene **4a** was treated under the reaction conditions, this mixture was recovered unaltered.



Scheme 2. Elimination from *syn*- or *anti*-**3a**

In conclusion, we have described a simple and general method for the stereoselective synthesis of highly functionalized and differently substituted terminal (*E*)-1,3-dienes from carbonyl compounds based on a cooperative catalytic indium/zinc system. The process is carried out through a sequential process involving an indium-promoted zinc-assisted chloroallylation followed by a zinc-mediated β-elimination. Both indium and zinc metalating agents are essential to efficiently afford the dienes from moderate to good yields and with good stereoselectivities. Studies aimed towards fully delineating the factors involved in this transformation and other synthetic applications of the products obtained are currently under investigation in our laboratory.

Experimental Section

All reagents were purchased in the highest quality available and were used without further purification. Column chromatography was carried out on silica gel 230-400 mesh. Compounds were visualized on analytical thin layer chromatograms (TLC) by UV light (254 nm) and potassium permanganate stain. NMR experiments were registered in an AV-Bruker spectrometer (^1H-NMR, 300 MHz, ^{13}C-NMR and DEPT-135, 75 MHz). Chemical shifts are given in ppm relative to the residual non deuterated solvent, which is used as an internal standard, and coupling constants (*J*) are reported in Hz. Diastereoisomeric ratios were obtained using ^1H-NMR (300 MHz) analysis of crude products. HRMS were measured at 70 eV using electrospray ionization in positive mode (ESI+).

General procedure for the synthesis of 1-substituted-1,3-dienes 4 from aldehydes 1

Indium trichloride (22 mg, 0.10 mmol), zinc dust (327 mg, 5.0 mmol) and sodium iodide (300 mg, 2.0 mmol) were added to a solution of the aldehyde **1** (1.0 mmol) and 1,3-dichloropropene (0.18 mL, 2.0 mmol) in $THF:H_2O$ (3:1, 10 mL). After refluxing the reaction mixture 12 h, it was filtered through celite, diluted with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and saturated aqueous sodium thiosulphate (25 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was then purified by flash column chromatography eluting with hexane except for **4h,j,l-m** where hexane/EtOAc 9/1 was used. The physical data of known dienes **4a-d,f-m** were comparable to those previously reported in the literature.[25-26,41-42] The physical data of the new diene **4e** are shown below.

(3*E*,10*Z*)-Trideca-1,3,10-triene 4e: 147 mg, Yield 82%. Colourless oil. R_f = 0.70 (hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 6.34 (dt, J = 17.0, 10.2 Hz, 1 H), 6.08 (dd, J = 15.3, 10.5 Hz, 1 H), 5.73 (dt, J = 14.6, 6.9 Hz, 1 H), 5.37 (q, J = 6.1 Hz, 2 H, H10, H11), 5.11 (dd, J = 16.9, 1.8 Hz, 1 H), 4.98 (dd, J = 9.8, 1.9 Hz, 1 H), 2.08 (dtd, J = 13.1, 6.8, 3.8 Hz, 6 H), 1.48–1.30 (m, 6 H), 0.99 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 135.4, 131.6, 130.9, 129.2, 114.6, 32.5, 29.6, 29.1, 28.8, 27.0, 20.5, 14.4 ppm. HRMS (ESI^+) $[M+H]^+$ calcd. for $C_{13}H_{23}$, 179.1794; found, 179.1793. IR (KBr, ν cm^{-1}): 1602, 1650 (-C=C-C=C-).

General procedure for the synthesis of 1,1-disubstituted-1,3-dienes 6 from ketones 5

Indium trichloride (22 mg, 0.10 mmol) (29 mg, 0.25 mmol), zinc dust (327 mg, 5.0 mmol) and sodium iodide (300 mg, 2.0 mmol) were added to a solution of the ketone **5** (1.0 mmol) and 1,3-dichloropropene (0.18 mL, 2.0 mmol) in dry THF (10 mL). After refluxing the reaction mixture 12 h, it was quenched with HCl (3 mL, 0.1 M), diluted with water (25 mL) and extracted with diethyl ether (3 x 25 mL). The organic material was then dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexane to afford dienes **6a-j**. The physical data of known dienes **6a-e,g-j** were comparable to those previously reported in the literature.[12e,43-46] The physical data of the new diene **6f** are shown below.

[(1*E*,3*E*)-1,3-Diphenyl-hexa-1,3,5-triene 6f: 105 mg, Yield: 45%. Colourless oil. R_f = 0.45 (hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.57–7.18 (m, 10H), 7.08 (d, J = 15.8 Hz, 1H, H1), 6.45 (d, J = 11.2 Hz, 1H, H4), 6.35–6.23 (m, 1H, H5), 6.20 (d, J = 16.1 Hz, 1H, H2), 5.34 (J = 17.9 Hz, 1H, H6) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.8, 137.6, 137.4, 134.5, 132.7, 132.6, 131.7, 129.9, 128.9, 128.6, 128.2, 127.5, 127.4, 126.4, 125.1, 118.4 ppm. HRMS (ESI^+) $[M+H]^+$ calcd. for $C_{18}H_{17}$, 233.1325; found, 233.1323. IR (KBr, ν cm^{-1}): 1598, 1650 (-C=C-C=C-).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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