Regio- and Stereoselective Heck α-Arylation of Cinnamyl Alcohols

Ilaria Ambrogio, Sandro Cacchi,* Giancarlo Fabrizi, Antonella Goggiamani, Simona Sgalla
Dipartimento di Chimica e Tecnologie del Farmaco, Università degli Studi 'La Sapienza', P. le A. Moro 5, 00185 Rome, Italy
Fax +39(06)49912780; E-mail: sandro.cacchi@uniroma1.it

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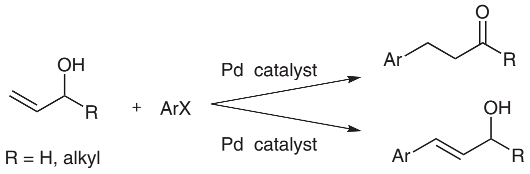
Abstract: The Heck reaction of cinnamyl alcohols with aryl iodides has been investigated using *n*-Bu_4NOAc as the base in toluene. Under these conditions, the reaction affords regio- and stereoselectively (*Z*)-2,3-diarylallylic alcohols in moderate to good yields. Experimental evidence suggests that the observed selectivity in formation of the vinylic substitution products is kinetic in origin under these conditions and that both the base and the solvent play a key role.

Key words: palladium, arylation, cinnamyl alcohols, Heck reaction

The palladium-catalyzed reaction of aryl halides with allylic alcohols unsubstituted at the β-carbon has been extensively investigated in the past years[1] and, depending on reaction conditions, has been shown to represent a useful tool for the preparation of β-aryl aldehydes and ketones or cinnamyl alcohol derivatives (Scheme 1). The new C–C bond is usually formed at the β-position with high regioselectivity.



Scheme 1

In contrast, the arylation of allylic alcohols containing a β-substituent has attracted much less attention and, after the pioneering and independent work of Heck[2] and Chalk[3] describing the formation of mixtures of arylated carbonyl derivatives in the reaction of halobenzenes with allylic alcohols bearing a terminal methyl group, there is little known on this chemistry. For example, treatment of cinnamyl alcohol with excess iodobenzene under an inert atmosphere or in the presence of air afforded mixtures of arylated products.[4] Formation of arylated cinnamyl alcohol and carbonyl derivatives was observed and the latter were isolated as the main components. The reaction showed also a strong tendency to generate the new C–C bond preferentially at the β-carbon under both conditions, though it appears to be more marked in the presence of air. The Heck arylation of β-substituted allylic alcohols with iodobenzene in molten *n*-Bu_4NBr was reported to give β-phenylated ketones as the main products with (*E*)-1,3-diphenyl-2-propen-1-ol and (*E*)-4-phenyl-3-buten-2-ol and a nonregioselective formation of phenylated aldehydes with crotyl alcohol.[5] The *cis*- and *trans*-crotyl alcohols were shown to undergo enantioselective phenylation to afford the corresponding β-phenyl aldehyde in low yield and ee using iodobenzene, $Pd(dba)_2$, and phosphinite-oxazoline ligands derived from D-glucosamine in the presence of Ag_2CO_3.[6] Recently, the reaction of the parent cinnamyl alcohol with aryl halides has been investigated in molten salts, showing that α-arylation is preferentially observed under these conditions.[7] However, a few examples were investigated and, in addition, the use of molten salts as the reaction medium may be inconvenient when scaling up is needed or in industrial applications. Therefore, the development of a simple and effective protocol to control the regio- and stereochemistry of this reaction would be desirable.

In this context, based on our long-standing interest in the Heck reactions of substituted olefins and our results in the arylation of α,β-unsaturated ketones,[8] methyl cinnamates,[9] acrolein dimethyl acetal,[10] the THP derivative of allyl alcohol,[11] and domino Heck reaction–cyclization processes[12] in the presence of *n*-Bu_4NOAc (which was found to play a key role in controlling the regio- and/or stereoselectivity of these reactions), we became interested in investigating more in detail this chemistry using the same base. Herein we report the results of this study.

Cinnamyl alcohols were prepared in 70–80% overall yields by a process involving a Heck reaction of aryl halides with methyl acrylate followed by treatment of the crude mixture containing the vinylic substitution product with DIBAL-H.[13]

Preliminary investigation into the process utilized 4-iodoanisole, a model of electron-rich aryl iodides, and cinnamyl alcohol. Reactions were carried out by using phosphine-free $Pd(OAc)_2$ as source of Pd(0) species. The product distributions obtained under a variety of conditions suggested that several competing processes were operating, including the arylation at the α- and β-olefinic carbons and oxidation processes. Some of the most significant results are summarized in Table 1.

Under Jeffery conditions[14] a mixture of α- and β-aryl derivatives was obtained with a slight preference for forming the new C–C bond at the β-carbon (Table 1, entry 1). Aldehydes **6a** and **7a** were isolated in 42% overall yield, **5a** (the likely precursor of **6a**) was not detected, and the arylated derivatives at the α-carbon **3a** and **4a** (its oxida-

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tion product) were isolated in 31% overall yield. Aldehyde products were the main components. The absence of detectable amounts of **5a** seems to imply that its oxidation under these reaction conditions is faster than that of **3a**. The stereochemistry of **3a** and **4a** was assigned by NOE experiments.

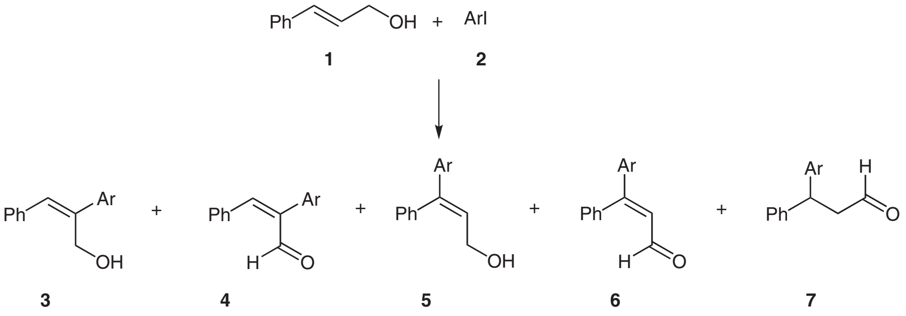
Using Et_3N as the base provided poor results. Both in DMF and in toluene the reaction afforded complex mixtures of aldehyde products, including condensed derivatives that we have not further investigated: **3a** (Table 1, entry 2) and **3a** and **6a** (Table 1, entry 3) were the sole products that could be clearly detected and isolated, albeit in low yields.

Notably, when the reaction was performed in the presence of n-Bu_4NOAc in DMF, a marked preference for the arylation at the α-carbon was observed, the α- to β-arylation ratio being 1.96 (Table 1, entry 4) as compared to 0.74 under Jeffery conditions (Table 1, entry 1). The arylated cinnamyl alcohol **3a** was isolated in 43% yield as single stereoisomer. Switching to n-Bu_4NOAc in toluene increased the α- to β-arylation ratio to 4.86 and **3a** was isolated in a satisfactory 60% yield (Table 1, entry 6). No evidence of its stereoisomer formation was attained.

These outcomes suggest that both the base and the solvent can play a key role in controlling the regiochemistry of the carbopalladation step and that in the presence of n-Bu_4NOAc and toluene the phenyl substituent exerts a stronger directing effect than the hydroxyl group does. A possible explanation is that the acetate ligand bound to palladium in a bidentate mode, as suggested by computational studies,[11] combined with an apolar solvent prevents the hydroxyl group from establishing a Pd–O bond in the π-complex preceding the formation of the carbopalladation adduct, thus inhibiting a coordination-controlled addition step. It follows that the reaction of the cinnamyl alcohol with the σ-aryl palladium complex formed in situ affords the π-complex **A** that is converted into the vinylic substitution products via the transition states **B** or **C**, with the transition state **B** being favored by the fact that it minimizes steric strain by locating the aryl residue on the less hindered end of the carbon–carbon double bond (Scheme 2).

It seems that using n-Bu_4NOAc in toluene has also the additional beneficial effect of limiting the oxidation processes. We have made only a partial investigation of the oxidation leading to the formation of **4a** and **6a**.[15] Their

Table 1 The Influence of Solvents, Bases, and Additives in the Palladium-Catalyzed Reaction of 4-Iodoanisole and Ethyl 4-Iodobenzoate with Cinnamyl Alcohol[a]



Entry	Aryl iodide **2**	Solvent	Base	Additive	Time (h)	Yield (%)				
						α-Arylation		β-Arylation		
						3	**4**	**5**	**6**	**7**
1	4-$MeOC_6H_4I$	DMF	$NaHCO_3$	n-Bu_4NCl	7.5	22	9	–	23	19
2	(**2a**)	DMF	Et_3N	–	24[c]	27		trace		
3		toluene	Et_3N	–	24[d]	11	–	–	9	–
4		DMF	n-Bu_4NOAc	–	3	43	4	8	12	4
5		DMF	n-Bu_4NOAc	n-Bu_4NCl	8	49	10	4	24	–
6		toluene	n-Bu_4NOAc		3	60	8	4	7	3
7		toluene	n-Bu_4NOAc	n-Bu_4NCl	3	62	–	4	10	5
8	4-$EtO_2CC_6H_4I$	toluene	n-Bu_4NOAc	–	28	30	3	–	–	–
9	(**2b**)	toluene	n-Bu_4NOAc	n-Bu_4NCl	28	57	8	–	6	–
10		toluene	n-Bu_4NOAc	n-Bu_4NCl	40[e,f]	52	–	–	11	–

[a] Unless otherwise stated, reactions were carried out under an argon atmosphere at 90 °C on a 0.732 mmol scale using cinnamyl alcohol (1 equiv), 4-iodoanisole or ethyl 4-iodobenzoate (1.5 equiv), $Pd(OAc)_2$ (0.03 equiv), base (2 equiv), and of n-Bu_4NCl (1 equiv, when added) in solvent (2 mL).

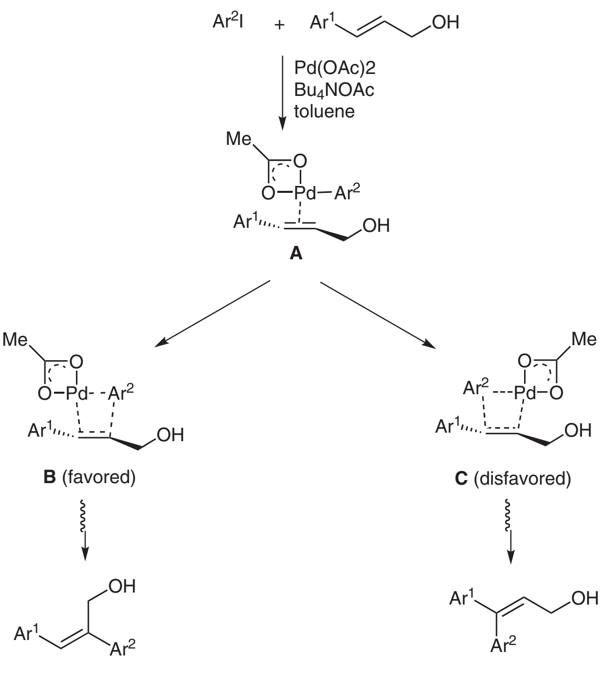
[b] Yields are given for isolated products.

[c] Aldehydes **4**, **6**, and **7** were obtained in 19% overall yield.

[d] Cinnamyl alcohol was recovered in 48% yield.

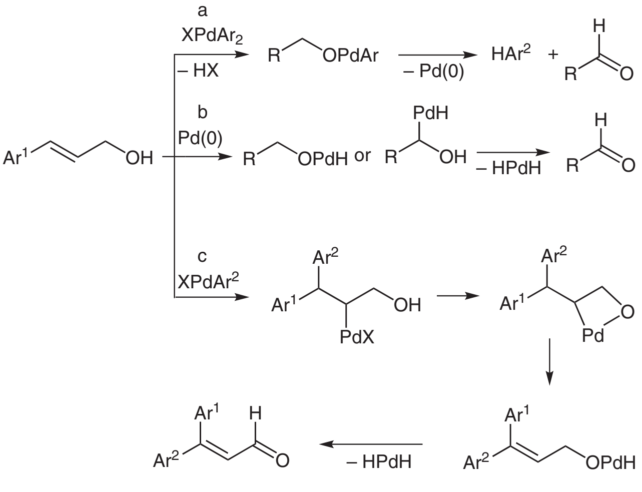
[e] In the presence of 2 equiv of n-Bu_4NCl.

[f] In the presence of 3 equiv of 4-$EtO_2CC_6H_4I$.



Scheme 2

formation via the reaction shown in Scheme 3 (path a)[16] appears unlikely because the reaction of 4-iodoanisole and cinnamyl alcohol under the conditions shown in entry 6 (Table 1) yielded only trace amounts of anisole, one of the products of the oxidation process. Even the involvement of atmospheric oxygen[17] was ruled out on the ground that careful deoxygenation of the reaction mixture did not produce appreciable changes in the reaction outcome. It seems therefore that oxidation products are generated through the oxidative addition of the corresponding allylic alcohols to Pd(0) species followed by the elimination of HPdH[18,19] (Scheme 3, path b) or (for compound **6a**) a palladaoxetane intermediate[20] (Scheme 3, path c).

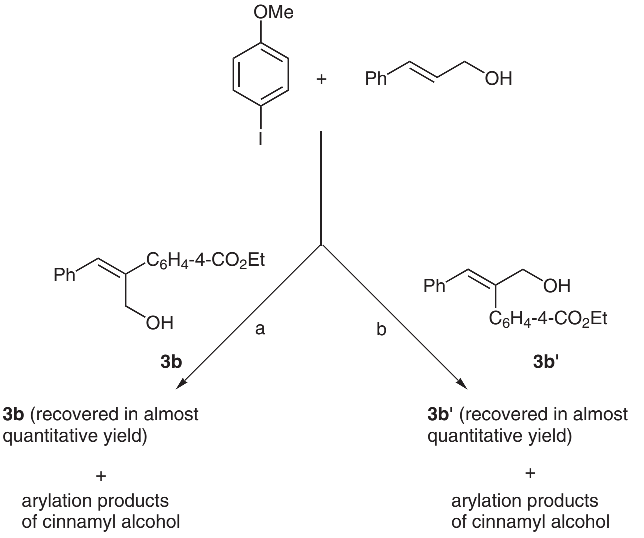


R = Ar^{1}CH=CH

Scheme 3

To determine whether the stereochemical outcome of the reaction might involve a kinetic-controlled process – which includes a regioselective *syn*-carbopalladation followed by a *syn*-β-elimination of HPdX species – or a thermodynamic process with an equilibration step following the initial elimination reaction, we carried out the following experiments. Cinnamyl alcohol and 4-iodoanisole were treated with *n*-Bu$_4$NOAc in toluene in the presence of a pure sample of **3b** (Scheme 4, path a). The product distribution and the overall yield of the arylation reaction were similar to those reported in Table 1, entry 6. Compound **3b** was recovered in almost quantitative yield and its stereochemistry was maintained. A similar result was obtained with the *E*-isomer **3b′** (Scheme 4, path b), prepared via Heck arylation of (*Z*)-3-phenyl-2-propen-1-ol[21] with ethyl 4-iodobenzoate under our standard conditions.

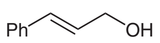
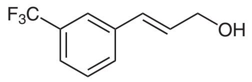
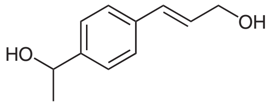
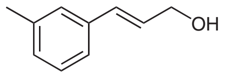
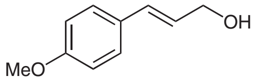
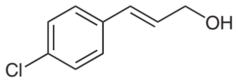
These results [including the formation of **3b′** from (*Z*)-3-phenyl-2-propen-1-ol] support the notion that under our conditions no stereochemical isomerization takes place after the β-elimination of HPd from carbopalladation adducts and that the stereoselectivity is consequently originated during the vinylic substitution process.



Scheme 4

When ethyl 4-iodobenzoate – a model of electron-poor aryl iodides – was treated with cinnamyl alcohol under the best conditions found for 4-iodoanisole, the corresponding vinylic substitution derivative **3b** was isolated only in 30% yield (Table 1, entry 8). Addition of ligands such as bipyridine, tris(2,4,6-trimethoxyphenyl)phosphine, P(*t*-Bu$_3$)$_3$ [added to the reaction mixture as HP(*t*-Bu$_3$)$_3$BF$_4$ salt][22] or utilization of the Herrmann catalyst gave unsatisfactory results. A remarkable increase of the yield was observed instead by adding *n*-Bu$_4$NCl (Table 1, entry 9). We then came back to 4-iodoanisole to investigate whether the addition of *n*-Bu$_4$NCl could give **3a** in higher yield. However, no distinctive advantages were observed. In contrast, the desired product was isolated in lower yield along with a significant amount of oxidation products in

Table 2 The Palladium-Catalyzed Reaction of Cinnamyl Alcohols with Aryl Iodides[a]

Entry	Cinnamyl alcohol **1**		Aryl iodide **2**		Time (h)	Yield (%) of (*Z*)-2,3-diarylallylic alcohol **3**[b]	
1		(**1a**)	4-$MeOC_6H_4I$	**2a**	3	**3a**	60
2	**1a**		4-$EtO_2CC_6H_4I$	**2b**	28[c]	**3b**	57
3		(**1b**)	4-$MeOC_6H_4I$	**2a**	24	**3c**	79
4	**1b**		4-$EtO_2CC_6H_4I$	**2b**	24	**3d**	51
5	**1b**		PhI	**2c**	24	**3e**	52
6		(**1c**)	4-$MeOC_6H_4I$	**2a**	24	**3f**	54
7	**1c**		3-MeC_6H_4I	**2d**	22	**3g**	56
8		(**1d**)	4-$MeOC_6H_4I$	**2a**	24	**3h**	47
9	**1d**		3-$MeOC_6H_4I$	**2e**	32	**3i**	46
10	**1d**		4-FC_6H_4I	**2f**	29	**3j**	44
11		(**1e**)	4-$MeOC_6H_4I$	**2a**	54	**3k**	60
12	**1e**		4-MeC_6H_4I	**2g**	22	**3l**	52
13		(**1f**)	4-MeC_6H_4I	**2g**	26	**3m**	58
14	**1f**		3-$MeOC_6H_4I$	**2e**	30	**3n**	68
15	**1f**		4-FC_6H_4I	**2f**	48	**3o**	56

[a] Unless otherwise stated, reactions were carried out under an argon atmosphere at 90 °C on a 0.732 mmol scale using cinnamyl alcohol (1 equiv), aryl iodide (1.5 equiv), $Pd(OAc)_2$ (0.03 equiv), and *n*-Bu_4NOAc (2 equiv) in toluene (2 mL).

[b] Yields are given for isolated products.

[c] In the presence of 1 equiv of *n*-Bu_4NCl.

DMF (Table 1, entry 5) whereas in toluene the yield of **3a** was only slightly higher (Table 1, entry 7). In addition, even the reaction of ethyl 4-iodobenzoate with **1b** did not afford better results in the presence of *n*-Bu_4NCl. Therefore, apart from the reaction of ethyl 4-iodobenzoate with cinnamyl alcohol, we decided to omit *n*-Bu_4NCl when we next extended the reaction to other aryl iodides and cinnamyl alcohols.[23] Nevertheless, it might be advisable to evaluate each time the effectiveness of using *n*-Bu_4NCl.

The results of our preparation studies are summarized in Table 2. Under our ‘optimal’ conditions, the reaction affords regio- and stereoselectively (*Z*)-2,3-diarylallylic alcohols in moderate to good yields with a variety of cinnamyl alcohols and electron-rich, electron-poor, and neutral aryl iodides.

In conclusion, we have shown that the reaction of cinnamyl alcohols with aryl iodides in the presence of *n*-Bu_4NOAc in toluene affords the corresponding α-arylated derivatives regio- and stereoselectively. Several pieces of experimental evidence suggest that the observed selectivity in formation of the vinylic substitution products is kinetic in origin under these conditions and that both the base and the solvent play a key role in controlling the reaction outcome. Although yields are only moderate to good, reaction conditions are simple, and the process may provide an easy access to this class of compounds.

Acknowledgment

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(13) **Typical Procedure for the Preparation of Cinnamyl Alcohols – Preparation of 1b**
A Carousel Reaction Tube (Radley Discovery), equipped with a magnetic stirrer, was charged with 1-(trifluoromethyl)-3-iodobenzene (1.0 g, 3,68 mmol), methyl acrylate (993 μL, 11,02 mmol), Et_3N (1.53 mL, 11.02 mmol), and $Pd(OAc)_2$ (24.8 mg, 0.11 mmol) in DMF (4 mL). The reaction mixture was warmed at 80 °C and stirred at the same temperature for 1.5 h under argon. After cooling, the reaction mixture was diluted with EtOAc, washed twice with a NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (4 mL), the resultant solution was cooled at –78 °C, DIBAL-H (1 M in hexane, 8 mL, 8.08 mmol) was added, and the reaction mixture was stirred at this temperature for 2 h under argon. After this time the reaction mixture was warmed at r.t., diluted with EtOAc, washed twice with a NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (*n*-hexane–EtOAc, 60:40) to afford 522 mg (70% yield) of **1b** as oil. IR (neat): 3343, 2925, 1440, 1332, 1124 cm^{-1}; ^1H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.63$ (s, 1 H), 7.55 (d, $J = 7.6$ Hz, 1 H), 7.50 (d, $J = 7.7$ Hz, 1 H), 7.45 (t, $J = 7.6$ Hz, 1 H), 6.67 (d, $J = 16.0$ Hz, 1 H), 6.45 (dt, $J_1 = 16.0$ Hz, $J_2 = 5.4$ Hz, 1 H), 4.37 (t, $J = 4.3$ Hz, 2 H), 1.61 (br s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.6$, 131.1 (q, $J = 33.0$ Hz), 130.7, 129.6, 129.4, 129.1, 124.20 (q, $J = 3.7$ Hz), 124.2 (q, $J = 272.3$ Hz), 123.19 (q, $J = 3.8$ Hz), 63.4. ^{19}F NMR (376.5 MHz, $CDCl_3$): $\delta = -62.8$. MS: *m/e* (rel. int.) = 202 (3) [M^+], 133 (12), 69 (100), 57 (21), 51 (18).

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(23) **Typical Procedure for the Preparation of (*Z*)-α-Arylcinnamyl Alcohols – Preparation of 3c**
A Carousel Reaction Tube (Radley Discovery), equipped with a magnetic stirrer, was charged with **1b** (60 mg, 0.297 mmol), 4-iodanisole (104 mg, 0.445 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol), and *n*-Bu_4NOAc (179 mg, 0.594 mmol) in toluene (1 mL). The reaction mixture was warmed to 90 °C and stirred at the same temperature for 24 h under argon. After this time the reaction mixture was diluted with EtOAc, washed twice with a NaCl solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 (*n*-hexane–EtOAc, 85:15) to afford 72 mg (79% yield) of **3c**. Mp 80–82 °C. IR (KBr): 3297, 2923, 1606, 1513, 1330 cm^{-1}. ^1H NMR (400.13 MHz, $CDCl_3$): $\delta = 7.68$ (s, 1 H), 7.63 (d, $J = 8.0$ Hz, 1 H), 7.56–7.54 (m, 4 H), 6.68 (d, $J = 12.0$ Hz, 2 H), 6.92 (s, 1 H), 4.67 (s, 2 H), 3.86 (s, 3 H), 1.58 (br s, 1 H). ^{13}C NMR (100.6 MHz,$CDCl_3$): $\delta = 159.6$, 141.0, 137.8, 132.3, 132.0, 130.7 (q, $J = 32.0$ Hz), 128.7, 128.1, 127.7, 125.6 (q, $J = 3.8$ Hz), 124.0 (q, $J = 272.6$ Hz), 123.7 (q, $J = 3.8$ Hz), 114.1, 60.1, 55.2. ^{19}F (376.5 MHz, $CDCl_3$): $\delta = -62.6$. MS: *m/e* (rel. int.): 308 (4) [M^+], 145 (4), 89 (12), 77 (16), 59 (100), 51 (26).

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