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Enantioselective C–C bond formation in styrene dimerization with chiral ansa zirconocene-based catalyst

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Abstract

In the presence of hydrogen and of (*R*,*R*)-ethylenebis tetrahydroindenyl zirconium dichloride activated by methylalumoxane, the styrene can be fully converted into low molecular weight compounds. The kinetic picture of the hydrooligomers formation is made complicated by the irregular regiochemistry of the styrene insertion. However the study on the effect of the feed composition on the products composition allows inferring mechanistic hypothesis and optimizing the formation of the chiral product, (*R*)-1,3-diphenylbutane. The subsequent functionalization of this molecule, without loss of chirality, discloses the potentiality of such kind of catalytic system for the synthesis of optically active synthones.

Keywords: Enantioselectivity; Ansa zirconocene; Hydrooligomer

1. Introduction

The synthesis of chiral C_2 symmetric ansa metallocenes of group 4 seemed disclose the opportunity of having components of catalysts for asymmetric synthesis [1]. Actually the greater amount of research on these systems deals with the stereospecific olefin polymerization and for this purpose the racemic mixture of ansa metallocenes works as well as the optical active ones [2]. An interesting exploitation of ansa zirconocenes in the asymmetric hydrogenation of tetrasubstituted olefins was reported by Buchwald et al. [3]. On the other hand the possibility of obtaining optically active low molecular weight compounds through propene [4] and higher olefins [5] polyinsertion was described by Pino et al. that were able to infer useful information on the stereocontrol mechanism of such polymerization catalysts from hydrooligomerization and careful analysis of the products. More recently we have reproduced this approach [6] in order to collect some information about the regiochemistry and stereochemistry of the styrene polyinsertion. This latter study suggested the use of the polyinsertion catalysis associated with chain-transfer by molecular hydrogen for the convenient synthesis of chiral molecules from styrene. Indeed an attempt to cover this was made by Waymouth and Pino [7] without success, while the same research group described the asymmetric styrene deuteration [8]. In this communication we report on the obtainment of optically active 1,3-diphenylbutane (1,3-dpb) through styrene hydro-oligomerization.

2. Results and discussion

The optically active catalyst we employed is the (*R*,*R*)-ethylenebis tetrahydroindenyl zirconium dichloride, (EBTHI)$ZrCl_2$ that, activated by methylalumoxane (MAO) and under H_2 pressure, gives rise to the cationic species (EBTHI)ZrH^+. The reaction conditions provide for the use of pure styrene as well as of toluene solution of styrene, under hydrogen pressure ranging between 1 and 40 atm, at 50 °C, up to complete styrene conversion.

The composition of the products mixture, according to Scheme 1, depends on the feed composition, and the amount of lower molecular weight products increases with increasing the H_2 pressure. Less obvious is the observation that the hydrodimers ratio 1,3-diphenylbutane/1,4-diphenylbutane (1,3-dpb/1,4-dpb) increases with increasing the $P(H_2)$/[styrene] in the feed, up to 0.4 for the highest values of hydrogen pressure (Fig. 1). Unfortunately with increasing the hydrogen pressure, the overall yield of hydrodimers decreases, due to the large production of ethylbenzene, that is of the monoinsertion product

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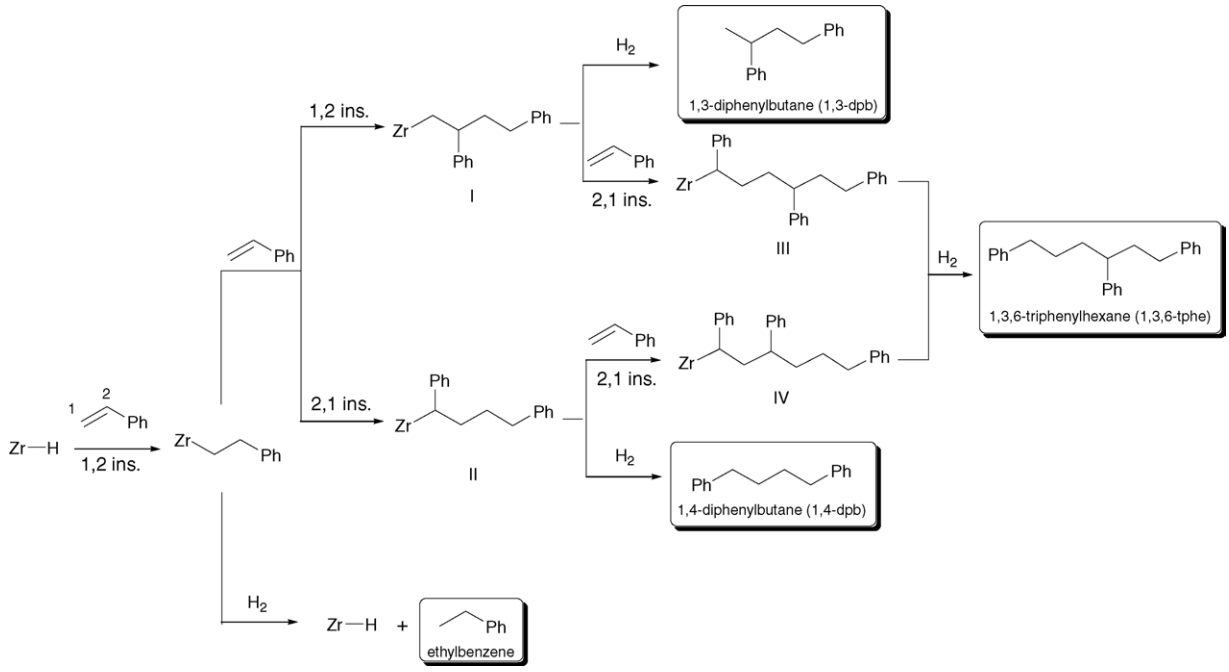


Scheme 1.

(Table 1). The limit value of this ratio we have observed is the measure of the regioselectivity of the styrene insertion into the zirconium–carbon bond and it indicates that the secondary insertion is about 2.5 times preferred with respect to the primary one. Nearly the same regioselectivity was observed [9] for the insertion into the zirconium–$^{13}CH_3$ of a C_S symmetric ansa zirconocene.

The observation (Fig. 1) that the hydrodimers ratio depends on the hydrogen pressure could be justified by assuming that, after the secondary styrene insertion (intermediate II of Scheme 1), the cut of the metal–carbon bond is nearly the sole possible event, whereas after the primary styrene insertion (intermediate I) the hydrogenolysis would compete with a further styrene insertion. Consequently, only after the primary styrene insertion, the feed composition could play a relevant role to determine whether the chain growth ends (high hydrogen pressure) or continues (low hydrogen pressure).

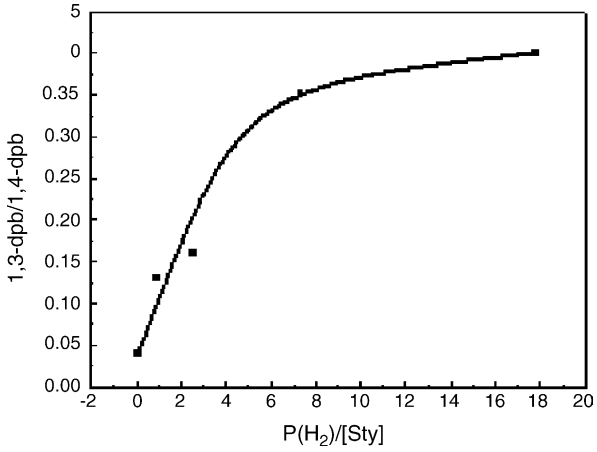


Fig. 1. Hydrodimers ratio as a function of the feed composition.

The above discussed high probability of the hydrogenolysis after secondary styrene insertion could be due either to the higher reactivity of such bond toward hydrogen, in accordance with the recent observations of Landis [10], or to its lower reactivity toward styrene insertion.

From the stereochemical point of view, the regioregular hydrodimer, 1,3 dpb, bears one stereogenic centre and shows an $[\alpha]_D = -11.6$ ($c = 15.7$, $CHCl_3$). By comparison with literature data [11], to the asymmetric carbon atom can be assigned the absolute configuration *R*. This clearly indicates that the *R*,*R* complex prefers the styrene enantioface *si* which points the aromatic ring away from the tetrahydroindenyl C6 ring, as depicted in Fig. 2. Such a result is in accordance with the enantioselectivity of this ansa zirconocene toward the propene [4] (actually the preferred propene enantioface is labelled *re*, but the descriptor changes because of the higher CIP priority of the phenyl group). On the contrary, for the secondary styrene insertion, the evidences reported in literature indicate the coordination of the opposite enantioface (*re*) both during polyinsertion [12] and in

Table 1
Relative amounts of hydrooligomers with different feed composition[a]

Entry	$P(H_2)$/[styrene]	1,4-dpb[b]	1,3-dpb[c]	1,3,6-tphe[d]
1	0.11	10.1	0.39	7.1
2	0.92	27.8	3.4	16.8
3	2.56	26.0	4.1	10.7
4	7.33	20.0	7.0	9.4
5	17.8	14.4	5.6	6.9

[a] Reaction conditions: $T = 50\,^{\circ}C$, MAO/(EBTHI)$ZrCl_2 = 1000$, styrene (40–200 mL), toluene (until 200 mL), $P(H_2)$ (range: 1–40 atm).
[b] Percentage of styrene converted into 1,4-diphenylbutane.
[c] Percentage of styrene converted into 1,3-diphenylbutane.
[d] Percentage of styrene converted into 1,3,6-triphenylhexane.

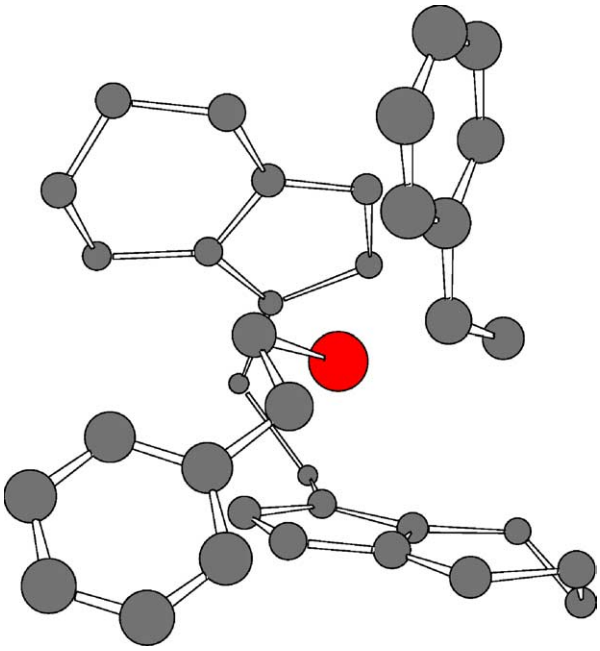


Fig. 2. Enantiofacial selectivity of the ansa zirconocene catalyst.

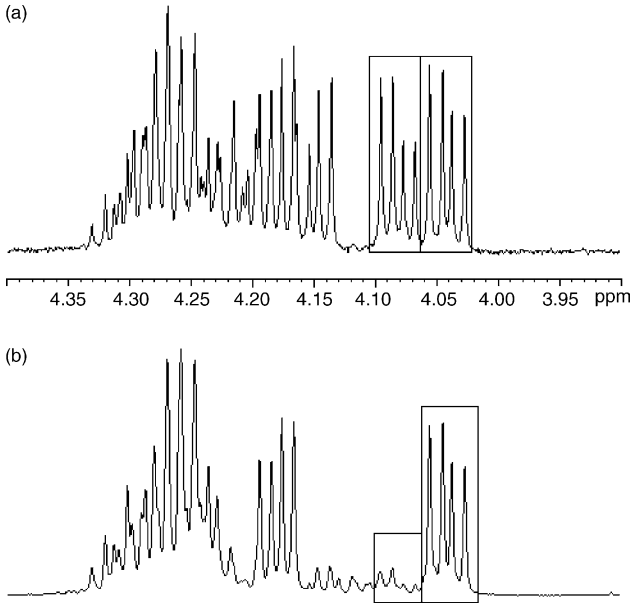
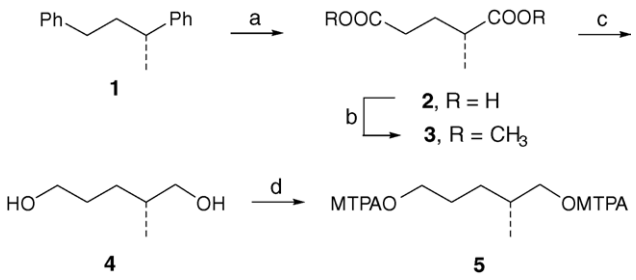


Fig. 3. ^{1}H NMR spectra of MTPA esters obtained starting from racemic diol **4** (a) and from diol obtained from **1** (b).

the monoinsertion with the chiral (EBTHI)Zr(η^2-pyrid-2-yl)$^+$ complex [13]. These stereochemical considerations strongly support the above regiochemical assumption that 1,3-dpb arises from double primary insertion, while the hypothesis of double secondary insertion can be rejected because it should afford the (*S*)-1,3-dpb.

In order to evaluate the enantiomeric excess (e.e.) we subjected the obtained 1,3-dpb to some manipulations (Scheme 2). Exposure of **1** to ruthenium tetraoxide catalyzed oxidation [14] afforded 2-methylglutaric acid (**2**). Methyl ester **3**, obtained after esterification of **2**, was then reduced to diol **4**. Finally, reaction of **4** with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA–Cl) afforded a mixture of MTPA ester diastereoisomers, useful [15] for the estimation of e.e. In fact, ^{1}H NMR spectrum of the mixture showed different chemical shift values for the methylene carbinol protons of the diastereoisomers (Fig. 3a). In this way, the e.e. of **4** was determined as 77% by integrating the resonance signals at δ 4.04 (major stereoisomer) and at δ 4.08 (minor stereoisomer) (Fig. 3b).



Scheme 2. Reagents and conditions: (a) AcOEt, CH_3CN, H_2O, $NaIO_4$, $RuCl_3$, 17 h, rt; (b) MeOH, conc. H_2SO_4, reflux, 3 h; (c) $LiAlH_4$, Et_2O, reflux, rt, 40% three steps; (d) (*S*)-MTPACl, DMAP, CH_2Cl_2, rt, 1 h, quant.

3. Conclusion

The approach we have exploited to obtain chiral molecules from unexpensive reagents, such as styrene and gaseous hydrogen, seems show interesting features: the considerable turnover and the good enantiomeric excess. The specificity towards the target we have obtained by using the commercially available chiral ansa zirconocene could be considerably improved by keeping in mind the wide library of such complexes and the spread of regiospecificity and stereospecificity they show [2,6].

It is worth to note that the scarce number of these C_2 symmetric complexes available as pure enantiomers could be expanded following the way recently described by LoCoco and Jordan [16] for the chelate-controlled enantioselective synthesis of ansa zirconocenes.

The analysis of the composition of the oligomers mixture and of the configuration of the chiral carbon, in the light of previous studies on the stereocontrol mechanism, indicates the styrene primary insertion into the Zr–H bond in the pathway affording 1,3-dpb.

4. Experimental part

4.1. Materials and general procedures

All the moisture sensitive operations were carried out under a nitrogen atmosphere by using standard Schlenk techniques. Dry solvents were freshly distilled. Toluene was refluxed 48 h over metallic sodium and distilled under a nitrogen atmosphere; Et_2O was distilled from $LiAlH_4$; CH_2Cl_2 was distilled from calcium hydride. Styrene (99% GC, Aldrich) was stirred 1 h over calcium hydride before distillation under reduced pressure of nitrogen. Methylalumoxane (MAO), provided by Witco as

30 wt.% solution in toluene, was dried before use by removing in vacuo the solvent.

(*R*,*R*)-ethylenebis tetrahydroindenyl zirconium dichloride [(EBTHI)$ZrCl_2$] was purchased from MCAT. The other materials and reagents, available from commercial suppliers, were generally used without further purification.

Flash chromatography was performed on Merck silica gel 60 (particle size: 0.040–0.063 mm).

The NMR spectra were recorded at room temperature on Bruker DRX 400 or Bruker DRX 300 spectrometers. Chemical shifts, in δ units (ppm), are reported relative to the residual solvent peak ($CHCl_3$: $\delta = 7.26$, $^{13}CDCl_3$: $\delta = 77.0$). ^{1}H NMR spectra for **5** were recorded on a Bruker DRX 600 spectrometer. The assignment of resonance signals in the ^{13}C NMR spectra of the hydrooligomers has been carried out through the additivity rules and through comparison with the literature data [6]. GC–MS measurements of the mixture of hydrooligomers were recorded on a GC Trace 2000 SERIES connected to Finnigan Thermoquest GLQ Plus 2000 spectrometer with an ion trap detector. Optical rotations were measured with a JASCO DIP-1000 polarimeter.

4.2. Styrene hydrooligomerization

Styrene hydrooligomerizations were carried out in a 250 mL steel autoclave, which was evacuated, then charged with a mixture of styrene, MAO and (*R*,*R*)-(EBTHI)$ZrCl_2$(Al/Zr in mol = 1000) and, when necessary, toluene. The autoclave was thermostated at 50 °C, fed with hydrogen at constant pressure (5, 8 or 40 atm) and mechanically shaken.

Styrene hydrooligomerizations at atmospheric pressure of hydrogen were performed in a 100 mL glass flask.

The reactions were stopped after 9 h by venting off the hydrogen and quenching the reaction mixture into acidified ethanol. By shaking with water, an organic phase was separated. The residue aqueous layer was extracted with *n*-pentane (3×). The combined organic phases were dried with Na_2SO_4 and filtered, then the *n*-pentane was removed under reduced pressure, at room temperature. The composition of the mixture, determined by GC–MS analysis, shows the complete consumption of the styrene but for the oligomerization carried out at atmospheric pressure (82.4% of unreacted styrene in Entry 1 of Table 1). Then a distillation under reduced pressure affords a fraction of ethylbenzene, the second fraction containing the mixture of hydrodimers, and the third one containing the 1,3,6-triphenilhexane (1,3,6-tphe). From the second fraction, most of 1,4-diphenilbutane (1,4-dpb) separates by spontaneous crystallization at room temperature (m.p. 52–54 °C). 1,3-Diphenylbutane was obtained through further fractionation by using a Vigreux column.

1,3,6-triphenylhexane. ^{13}C NMR (400 MHz, $CDCl_3$) δ: 29.5 (C-2), 34.0 (C-6), 36.1 (C-1), 36.8 (C-3), 38.7 (C-5), 45.6 (C-4), the aromatic C atoms resonate between 125.8 and 145.5. MS: 314 (M^+).

1,4-diphenylbutane. ^{13}C NMR (400 MHz, $CDCl_3$) δ: 31.3 (C-2), 36.0 (C-1), the aromatic C atoms resonate between 125.8 and 145.5. MS: 210 (M^+).

1,3-diphenylbutane. ^{13}C NMR (400 MHz, $CDCl_3$) δ: 22.7 (C-4), 34.1 (C-1), 39.7 (C-3), 40.2 (C-2), the aromatic C atoms resonated between 125.8 and 147.5. MS: 210 (M^+). $[\alpha]_D = -11.6$ ($c = 15.7$, $CHCl_3$); [9] $[\alpha]_D$: $= -15.6$ ($c = 15.7$, $CHCl_3$).

4.3. Determination of enantiomeric excess of 1,3-(R)-diphenilbutane (*1*)

4.3.1. Synthesis of diol *4*

To a stirred solution of 1,3-diphenylbutane (**1**) (1.50 g, 7.14 mmol) in EtOAc (16.3 mL), CH_3CN (16.3 mL) and H_2O (163.0 mL) were added $NaIO_4$ (38.2 g, 178.4 mmol) and $RuCl_3$ (74.6 g, 0.36 mmol). The reaction mixture was stirred at room temperature for 21 h and then extracted with EtOAc (3× 200 mL). The combined organic phase were dried over Na_2SO_4, filtered and concentrated under reduced pressure, affording 0.600 g of crude dicarboxylic acid **2**, which was used in the subsequent reaction without purification.

To a solution of **2** in MeOH (20 mL) conc. H_2SO_4 (0.20 mL) was added and the resulting reaction mixture was refluxed overnight with stirring, under a nitrogen atmosphere. Then, it was allowed to cool to room temperature and quenched by addition of a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with *n*-pentane (3× 50 mL) and with Et_2O (3× 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure yielding 0.650 g of crude **3**, employed in the next reaction step without purification.

A solution of crude **3** in dry Et_2O (5.0 mL) was added dropwise to a solution of $LiAlH_4$ (0.190 g, 5.0 mmol) in dry Et_2O (5.0 mL), under nitrogen. At once, Et_2O reflux started and the mixture was vigorously stirred for 1 h. Then mixture was carefully quenched with AcOEt (3.0 mL) at 0 °C. HCl 1N (2.0 mL) was added and the organic phase was separated. The aqueous phase was further extracted with AcOEt (3× 4.0 mL) and the combined organic phases, washed with a saturated aqueous $NaHCO_3$ solution and with brine, were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford 0.400 g of crude diol 4. The crude diol was flash-chromatographed (70–100% ethyl acetate in petroleum ether) to afford **4** (0.338 g, 40% on three steps).

4: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (3H, d, $J = 6.7$ Hz, CH_3CH), 1.10–1.67 (5H, m, $CH_2CH_2CHCH_3$, $CH_2CH_2CHCH_3$ and CH overlapped), 2.67 (2H, bs, OH × 2), 3.44 (2H, d, $J = 6.0$ Hz, $HOCH_2CH$), 3.61 (2H, t, $J = 6.1$ Hz, CH_2CH_2OH).

^{13}C NMR (300 MHz, $CDCl_3$) δ: 16.5 (q), 29.0 (t), 29.7 (t), 35.3 (d), 62.8 (t), 67.8 (t). $[\alpha]_D = +8.4$ ($c = 1.68$, Et_2O); [17] $[\alpha]_D = +10.7$ ($c = 1.68$, Et_2O).

4.3.2. Synthesis of MTPA ester derivative *5*

To a solution of **4** (0.010 g, 0.083 mmol) in a 1.0 mL of dry CH_2Cl_2, DMAP (0.081g, 0.66 mmol) and (*S*)-MTPA–Cl (62.0 μL, 0.33 mmol) were added. The reaction was stirred for 1 h at room temperature. The reaction mixture was then passed through a short column of silica gel, which was fur-

ther eluted with Et_2O (10 mL). The eluent was concentrated to give the desired crude di-(*R*)–MTPA ester as a colorless oil. The enantiomeric excess was determined as 77% by direct ^1H NMR analysis of this crude by integrating the resonance signals at δ 4.04 (1H, dd, $J = 6.3$, 10.8 Hz, (*R*)–MTPA–OCH*H*CH– for the major diasteroisomer **5**) and at δ 4.08(1H, dd, $J = 5.6$, 10.8 Hz, (*R*)–MTPA–O–CH*H*CH– for the minor diasteroisomer) (Fig. 3b). ^1H NMR spectrum of the di-(*R*)-MTPA esters, derived from racemic **4**, is reported in Fig. 3a.

The reaction was monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and spraying with *p*-anysaldehyde–EtOH–H_2SO_4–AcOH solution and drying.

5: ^1H NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, d, $J = 6.6$ Hz, C*H*$_3$CH), 1.17 (1H, m, CH*H*CHCH$_3$), 1.34 (1H, m, C*H*HCHCH$_3$), 1.61–1.74 (2H, m, CH*H*CH$_2$O–MTPA and C*H*HCH$_2$O–MTPA overlapped), 1.82 (1H, m, C*H*), 3.53 (6H, s, C*H*$_3$O × 2), 4.04 (1H, dd, $J = 6.3$, 10.8 Hz, MTPA–OCH*H*CH), 4.18 (1H, dd, $J = 5.8$, 10.8 Hz, MTPA–OC*H*HCH), 4.22–4.31 (2H, m, MTPA–OC*H*HCH$_2$ and MTPA–OCH*H*CH$_2$ overlapped), 7.40 (6H, m, Ar*H*), 7.49 (4H, m, Ar*H*).

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