

Short Note

Dibenzyl-(1*S*^{*},2*S*^{*})-2,3-dihydro-1*H*-indene-1,2-dicarboxylate

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Abstract: The synthesis of dibenzyl-(1*S*^{*},2*S*^{*})-2,3-dihydro-1*H*-indene-1,2-dicarboxylate has been realized through a diastereospecific bis-alkoxycarbonylation reaction, which starts from the cheap and easily available 1*H*-indene, benzyl alcohol, and carbon monoxide. The catalyst is formed in situ by mixing Pd(TFA)₂, the ligand *N*²,*N*³-bis(2,6-dimethylphenyl)butane-2,3-diimine, *p*-benzoquinone is used as an oxidant, and benzyl alcohol acts both as a nucleophile and as the main solvent.

Keywords: homogeneous catalysis; carbonylation; bis-alkoxycarbonylation; palladium; aryl α -diimine ligand; succinic acid ester; succinates

1. Introduction

The most commonly used processes for the synthesis of carbonylated compounds are probably carbonylation reactions [1–3]. In particular, the bis-alkoxycarbonylation of olefins [4–6] is a very useful reaction for the synthesis of succinic acid ester derivatives, which are compounds that find applications in various industrial fields [7,8], including cosmetics [9] and food industries [10]. Through this process, in the presence of CO and alcohol, cheap functionalized alkenes can be easily converted into the desired succinate in one-step. The reaction is usually palladium-catalyzed and requires an oxidant for regenerating the catalytic active species [5,11]. Various bis-alkoxycarbonylations of olefins, using different conditions and catalytic systems, have been reported in the literature [12,13]. However, the main problems that emerge from these examples are represented by the limited scope of the processes described, in particular regarding the alcohols, and by the drastic reaction conditions usually required (high temperatures and/or high CO pressures). Recently, we have realized an efficient method for the bis-alkoxycarbonylation of variously functionalized olefins, utilizing aryl α -diimine/palladium(II) complexes as catalysts and *p*-benzoquinone as the oxidant [14–18]. Here, with the aim of broadening the scope and the applications of our developed bis-alkoxycarbonylation reaction of internal olefins, we have described the synthesis of dibenzyl-(1*S*^{*},2*S*^{*})-2,3-dihydro-1*H*-indene-1,2-dicarboxylate **3**.

2. Results and Discussion

Recently, we have reported the bis-alkoxycarbonylation of 1,2-disubstituted olefins [15]. The catalyst was formed in situ by mixing Pd(TFA)₂ and the ligand *N*²,*N*³-bis(2,6-dimethylphenyl)butane-2,3-diimine **1a**, which displays a 1,4-diaza-1,3-butadiene skeleton bearing two methyl groups and *ortho*-disubstituted aromatic rings linked to nitrogen atoms. The reaction proceeded in the presence of 1.5 equiv of *p*-benzoquinone as oxidant and 2 mol% of *p*-toluenesulfonic acid, under mild conditions (room temperature and 4 bar of CO pressure) and a mixture of alcohol/THF in a 7:1 ratio was employed as the solvent. Remarkably, the process was diastereospecific, therefore, starting from the (*E*)-alkene or the (*Z*)-alkene, diastereoisomers were obtained. Applying these conditions to the bis-alkoxycarbonylation of 1*H*-indene, bearing a C=C double bond in a (*Z*)-fashion, and utilizing benzyl alcohol,



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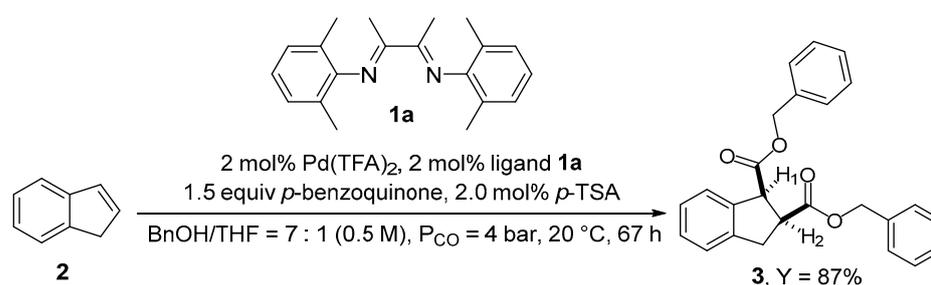
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product **3** was obtained in 87% isolated yield, as shown in Scheme 1. In this reaction, the benzyl alcohol acts as both the nucleophile and the main solvent. Its removal from the reaction mixture, after completion of the reaction, is difficult due to its high boiling point and poor water solubility, therefore more than one chromatographic column may be required for the isolation of the pure product. The proposed catalytic cycle accounting for the synthesis of compound **3** is illustrated in the Supplementary Materials [19]. The diastereospecificity of the reaction can be explained as a consequence of a concerted *syn* addition of the Pd-benzoyloxycarbonyl moiety to the olefin double bond [15]. The relative *syn* stereochemistry in product **3** was further validated by a (¹H,¹H)-NOESY (Nuclear Overhauser Effect SpectroscopY) experiment, which evidenced the presence of a NOE correlation between H₁ and H₂ (see Supplementary Materials). Moreover, the value of the *J* coupling constant of the doublet relative to H₁ (see Scheme 1) is 8.3 Hz, which is in agreement with that reported for similar substrates with the stereochemistry assigned [11].



Scheme 1. Pd-catalyzed bis-alkoxycarbonylation of indene using benzyl alcohol. Only one enantiomer is shown.

Other analyses, which confirm the structure of **3**, such as ¹³C-NMR and the ESI-MS spectrum, can be found in the Supplementary Materials.

The DFT calculated free Gibbs energy associated with the process resulted to be −39.1 kcal/mol, indicating that the whole process is highly exergonic (see Supplementary Materials).

3. Materials and Methods

Chemicals and instruments. The reaction was carried out under a carbon monoxide atmosphere ($P_{CO} = 4$ bar) with dry solvent under anhydrous conditions, in a stainless-steel autoclave, by using the Schlenk technique. The reaction was monitored using ¹H NMR by collecting a direct sample of the crude mixture. The ¹H NMR and ¹³C NMR were recorded on a Bruker Avance 400 spectrometer (¹H: 400 MHz, ¹³C: 101 MHz), using deuterated DMSO as the solvent. Chemical shifts are reported in the δ scale relative to the central line of the residual DMSO (2.50 ppm) for ¹H NMR and to the central line of DMSO (39.52 ppm) for ¹³C NMR. The ¹³C NMR was recorded with ¹H broadband decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, br = broad, d = doublet, dd = doublet of doublets, and m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). The elemental analysis was performed with a Thermo Finnigan Flash 1112 EA CHN analyzer. The ESI-MS spectrum was recorded on Waters Micromass ZQ 4000, using electrospray ionisation techniques, with the sample dissolved in MeOH. Carbon monoxide (Cp grade 99.99%) was supplied by Air Liquide (carbon monoxide is a toxic gas with potentially lethal action, adequate precautions must, therefore, be observed). The *p*-benzoquinone was purchased by Alfa Aesar and was filtered through a plug of silica gel washing with CH₂Cl₂, obtaining a yellow solid after drying the solution under vacuum. The pure compound **3** was isolated through flash column chromatography on silica gel 60 (40–60 μ m, 230–400 mesh). 1*H*-Indene **2** was purchased from Merck Sigma-Aldrich and, before use, was filtered through a plug of neutral Al₂O₃ without further purification. Anhydrous THF was distilled from sodium-benzophenone. The benzyl alcohol was dried over molecular sieves (Alfa Aesar, 4 Å, 1–2 mm, beads). Pd(TFA)₂ was purchased by

Fluorochem and *p*-toluenesulfonic acid was purchased from Merck Sigma-Aldrich and used without further purification. The ligand **1a** was synthesized according to the literature [20]. All solid reagents were weighted in an analytical balance without excluding moisture and air.

Computational Details. All DFT calculations have been performed using the ORCA 4.2.1 suite of quantum chemistry programs [21,22]. Geometries were optimized in vacuum using the Becke–Perdew (BP) functional [23,24] and the def2-TZVP basis [25]. Vibrational frequencies were calculated at the optimized geometries to check the stability of the stationary points and to evaluate the vibrational contribution to free energies at 298K. Final single point energy calculations at the optimized geometries were performed with the large def2-QZVPP basis [25] and the M06 functional [26], with the inclusion of solvation effects (with THF as solvent) through the SMD model [27] and of dispersion interactions [28]. The final free energy of each structure, used to evaluate the reaction free energy, was built by summing the difference between the def2-TZVP electronic and free energies to the def2-QZVPP single point electronic energy.

Synthesis of dibenzyl-(1*S,2*S**)-2,3-dihydro-1*H*-indene-1,2-dicarboxylate.** In a nitrogen flushed Schlenk tube, equipped with a magnetic stirring bar, 1*H*-indene **2** (2 mmol) and benzyl alcohol (3.5 mL) were added in sequence. The mixture was left under stirring for 10 min. In another nitrogen-flushed Schlenk tube, equipped with a magnetic stirring bar, the Pd(TFA)₂ (13.3 mg, 0.04 mmol) and THF (0.5 mL) were added in sequence. After the mixture turned into a red-brown color (20 min), the ligand **1a** (12.8 mg, 0.044 mmol) was added. The mixture was left under stirring for 10 min, turning into a dark orange color. The olefin solution and the formed catalyst were injected in sequence in a nitrogen flushed autoclave, equipped with a magnetic stirring bar, containing *p*-benzoquinone (325 mg, 3 mmol) and *p*-TSA·H₂O (7.6 mg, 0.04 mmol). After 10 min of stirring, the autoclave was flushed three times with CO and pressurized with 4 bar of carbon monoxide. The reaction was vigorously stirred at room temperature (20 °C) for 66 h. The autoclave was vented off and flushed with nitrogen and the crude was dried under reduced pressure and filtered through a plug of silica gel, washing with CH₂Cl₂/Et₂O = 1:1 (150 mL). The solution was dried up in vacuum and then NaOH 1 M (30 mL) was added and the solution was extracted with CH₂Cl₂ (3 × 30 mL). The combined organic solution was dried over Na₂SO₄ and the solvent was removed under reduced pressure. Product **3** was eventually obtained after column chromatography on silica gel (Petroleum Ether/CH₂Cl₂ 80: 20 to 50:50). Yield: 87% (671 mg), white solid.

*R*_f = 0.23 (Petroleum Ether/CH₂Cl₂ = 50:50). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.40–7.27 (m, 10H, ArH), 7.27–7.16 (m, 4H, ArH), 5.06 (d, *J* = 12.5 Hz, 1H, CH₂Ph), 4.98 (d, *J* = 12.5 Hz, 1H, CH₂Ph), 4.93 (s, 2H, CH₂Ph), 4.39 (d, *J* = 8.3 Hz, 1H, CHCH), 3.88–3.78 (m, 1H, CH₂CHCH), 3.38 (dd, *J* = 15.8, 9.7 Hz, 1H, CH₂CH), 3.16 (dd, *J* = 15.8, 8.9 Hz, 1H, CH₂CH). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 171.9 (C=O), 171.5 (C=O), 142.2 (C_{q,Ar}), 139.3 (C_{q,Ar}), 135.9 (C_{q,Ar}), 135.7 (C_{q,Ar}), 128.4 (CH_{Ar}), 128.3 (CH_{Ar}), 128.03 (2C, CH_{Ar}), 128.00 (CH_{Ar}), 127.98 (CH_{Ar}), 127.7 (CH_{Ar}), 126.8 (CH_{Ar}), 124.9 (CH_{Ar}), 124.6 (CH_{Ar}), 65.9 (CH₂Ph), 65.7 (CH₂Ph), 51.7 (CHCH), 46.3 (CH₂CHCH), 33.8 (CH₂CH). ESI-MS: *m/z* = 387 [M + H]⁺; *m/z* = 404 [M + NH₄]⁺; *m/z* = 409 [M + Na]⁺. Anal. for C₂₅H₂₂O₄ (386.45): calculated C 77.70, H 5.74; found C 77.3, H 5.6.

4. Conclusions

In conclusion, the bis-alkoxycarbonylation of the 1*H*-indene using benzyl alcohol has been successfully realized, leading to the diastereospecific synthesis of the succinic acid ester dibenzyl-(1*S**,2*S**)-2,3-dihydro-1*H*-indene-1,2-dicarboxylate. This palladium(II)-catalyzed reaction proceeds under mild reaction conditions (4 bar of CO at 20 °C) and the Δ_rG of the reaction has been evaluated through DFT calculations. The product has been fully characterized using NMR and ESI-MS analysis.

Supplementary Materials: Scheme S1: Proposed catalytic cycle. Only one enantiomer is shown; Figure S1: ^1H -NMR spectrum; Figure S2: ^{13}C -NMR spectrum; Figure S3: DEPT 135 (CH and CH_3 positive, CH_2 negative); Figure S4: COSY spectrum; Figure S5: HSQC spectrum; Figure S6: NOESY spectrum; Figure S7: Zoom of the NOESY spectrum (from 6.0 ppm to 2.0 ppm for both f1 and f2). Observed NOE correlation for H_1 (4.39 ppm) and H_2 (3.83 ppm); Figure S8: ESI-MS (ESI+) spectrum of compound **3**.

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